ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 January 19; 11(1): 1-26



Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Yu-Jie Ma*.

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
January 19, 2021

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ONLINE SUBMISSION
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World J Psychiatr 2021 January 19; 11(1): 1-12

DOI: 10.5498/wjp.v11.i1.1

ISSN 2220-3206 (online)

OPINION REVIEW

How to construct neuroscience-informed psychiatric classification? Towards nomothetic networks psychiatry

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Author contributions: The authors declare equal contribution to this manuscript.

Conflict-of-interest statement: None to declare.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Bulgaria

Peer-review report's scientific quality classification

Grade A (Excellent): 0

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Abstract

Psychiatry remains in a permanent state of crisis, which fragmented psychiatry from the field of medicine. The crisis in psychiatry is evidenced by the many different competing approaches to psychiatric illness including psychodynamic, biological, molecular, pan-omics, precision, cognitive and phenomenological psychiatry, folk psychology, mind-brain dualism, descriptive psychopathology, and postpsychiatry. The current "gold standard" Diagnostic and Statistical Manual of Mental Disorders/International Classification of Diseases taxonomies of mood disorders and schizophrenia are unreliable and preclude to employ a deductive reasoning approach. Therefore, it is not surprising that mood disorders and schizophrenia research was unable to revise the conventional classifications and did not provide more adequate therapeutic approaches. The aim of this paper is to explain the new nomothetic network psychiatry (NNP) approach, which uses machine learning methods to build data-driven causal models of mental illness by assembling risk-resilience, adverse outcome pathways (AOP), cognitome, brainome, staging, symptomatome, and phenomenome latent scores in a causal model. The latter may be trained, tested and validated with Partial Least Squares analysis. This approach not only allows to compute pathway-phenotypes or biosignatures, but also to construct reliable and replicable nomothetic networks, which are, therefore, generalizable as disease models. After integrating the validated feature vectors into a well-fitting nomothetic network, clustering analysis may be applied on the latent variable scores of the R/R, AOP, cognitome, brainome, and phenome latent vectors. This pattern recognition method may expose new (transdiagnostic) classes of patients which if cross-validated in independent samples may constitute new (transdiagnostic) nosological categories.

Key Words: Psychiatry; Major depression; Mood disorders; Schizophrenia; Antioxidants; Oxydative stress

Grade B (Very good): B, B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: November 24, 2020
Peer-review started: November 24, 2020
First decision: December 12, 2020
Revised: December 15, 2020
Accepted: December 26, 2020
Article in press: December 26, 2020
Published online: January 19, 2021

P-Reviewer: Cheng J, Tcheremissine OV
S-Editor: Gao CC
L-Editor: A
P-Editor: Li JH

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Core Tip: The nomothetic network psychiatry approach is a new method which aims to construct causal models of schizophrenia and mood disorders by integrating all features of those mental illnesses into a data-driven model. These features comprise data on risk-resilience, adverse outcome pathways, the cognitome, brainome, symptomatome, staging, and the phenomenome. Partial Least Squares analysis may be employed to train, test, and validate those models and to build pathway-phenotypes or biosignatures. Clustering analysis performed on all illness features, reduced into latent traits scores, may expose relevant new transdiagnostic classes.

Citation: Stoyanov D, Maes MH. How to construct neuroscience-informed psychiatric classification? Towards nomothetic networks psychiatry. *World J Psychiatr* 2021; 11(1): 1-12
URL: https://www.wjgnet.com/2220-3206/full/v11/i1/1.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i1.1

INTRODUCTION

For the past 200 years, psychiatry remained a discipline plagued by conceptual controversies, whose roots go back to its poor ontological and epistemological foundations[1]. Psychiatry remained in a permanent state of crisis due to methodological mistrust in psychiatric case definitions, which fragmented psychiatry from the field of medicine[2]. The crisis is psychiatry is further evidenced by the many different competing approaches and ways to understand mental and psychiatric disorders including the etiological approach of psychodynamic psychiatry, biological, molecular, pan-omics, and precision psychiatry, cognitive psychiatry, folk psychology, the mind-brain dualism, descriptive psychopathology, postpsychiatry, and phenomenological psychiatry. Moreover, the gold standard taxonomies used to diagnose mood disorders and schizophrenia are not reliable[3,4].

Recently, we employed a new approach, namely the nomothetic network psychiatry (NNP) approach, which uses machine learning methods to build new data-driven models of mood disorders and schizophrenia using all features of those disorders including etiological, context centered hermeneutic, biological, molecular, cognitive, descriptive psychopathological, and phenomenological features[3-7]. The aim of this opinion paper is to review how to build nomothetic networks using Partial least Squares (PLS) analysis and how to expose new classifications of these disorders using unsupervised pattern recognition techniques.

FOLK PSYCHOLOGY

Folk or commonsense psychology tries to explain the mental state of individuals including symptoms, cognitions, or behaviors as the outcome of everyday life psychology and daily life experiences such as pleasure, sensations, pain, common beliefs, perceptions, *etc*.[8]. Folk psychology narratives are embodied in psychiatric inventories, either observational interviews or self-evaluation scales, which are supposed to deliver meaningful information intended to contribute to the diagnostic criteria of the conventional psychiatric classification systems or to rating scales that measure severity of illness. Thus, structural components of current psychiatric inventories are decomposed into items (statements and questions) some of which are formulated in a folk psychology-like language. For example, items such as "I cry easily" or "I feel down and depressed" are borrowed from folk psychology. In a futile effort to translate these symptoms into a more technical and medical jargon, such as depressive mood for instance (anhedonia and dysthymia), those items are then scored on a 4- or 7-degrees Likert scale so that the total score may resemble a statistically digestible entity. In this manner, common sense folk psychology expressions are converted into "diagnostic" statements without any reference to independent validators. The most common "state" dependent clinical measures or inventories in psychiatry remain folk psychology narratives with some window dressing for

statistical purposes. What is missing in such perspective is the biological, neuronal, and cognitive basis to better understand the existing phenomena in psychopathology, which is declared on the agenda of post-modern psychiatry.

MIND-BRAIN AND MIND-BODY DUALISM

There are two main intellectual frameworks which outline the rationale behind the scientific enterprise in psychiatry. The first is psycho-physical dualism which is supposed to drive the advances in psychotherapy and psychosocial interventions in mental illness. Mind-body dualism is the theory which proposes that mental phenomena are non-physical or that not all mental processes are physical. As such, mind and body would be, at least in part, separable entities[9,10]. The common psychiatric approach is essentially focused on what might be described as "mind" in terms of the mind-brain debate.

The second is the physicalism stance, which considers that everything is physical[11]. Physicalism and materialism are implicated as a primary assumption in influential advances in psychiatric research including biological, molecular, and pan-omics psychiatry, functional neuroimaging, and cognitive science[12].

LOCALIZATIONISM AND DYNAMIC PSYCHIATRY

Early efforts initiated by the Wilhelm Griesinger and the Wernicke-Kleist-Leonhard schools tried to consolidate psychiatric nosology using organic etiological factors[13]. These early theories, associated with the notions of localizationism, culminated in the works of Karl Wernicke and Karl Kleist and Maynert-Wernicke's connectionism. Psychodynamic theories, initiated by Sigmund Freud, and later versions of psychoanalysis, applied a conceptual organization of psychiatric syndromes based on a psychodynamic etiologic approach but remained grounded on the tacit assumptions of psychophysical dualism. However, attempts to bring together the disparate etiological explanatory models of psychodynamic paradigms and localizationism and clinical diagnoses proved to be inefficient. Neither of those views offered consolidated and sustainable pictures of psychiatric diagnoses applicable in the medical practice.

DESCRIPTIVE AND PHENOMENOLOGICAL PSYCHIATRY

Descriptive psychopathology or psychiatry focusses on readily observable behaviors and symptoms, rather than on underlying psychoanalytic or organic etiologies. Phenomenological psychopathology focuses on the patients subjective, own lived experiences of selfhood, space, time, body, and mind[14].

Current gold standard psychiatric classifications are based on descriptive and phenomenological psychopathology, including the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) taxonomies. These case definitions are derived from cross-culturally diverse, even sometimes unique criteria[15], established *ex convention* by professional bodies like the American Psychiatric Association (APA) and the World Health Association (WHO). These *ex consensus-based* case definitions of nosological psychiatric classes use de-contextualized narratives and descriptive features of the disorder derived from folk psychology-like self-reports by the patient and observer-based interviews[16].

Due to the missing etiological and biomarker foundations, one crucial limitation of the current classifications, such as DSM-5 and ICD-10, is their top-down manner of generation[3-5,16]. The structured interviews, which are used to construct diagnostic categories, pre-define the clinical diagnosis before other tests are performed, including etiologic, state and trait-biomarkers, brain imaging, and cognitive probes. In that regard the diagnosis remains based on controversial and value laden statements, whereas the causal and biological measures are supposed to be concomitant data, either supporting the diagnosis or not. However, no falsification or dispute of the diagnostic assumption is possible based on information from outside the data source of the clinical interview, thus precluding a top-down deductive approach[3-5]. It should be added that those professional bodies are most often under the influence of para-motivation from the pharmaceutical industry or other confounds which leads to deeply controversial and in the end of the day counter-productive debates on the

existence of specific case definitions of psychiatric illness.

Moreover, the taxonomies used to make the diagnosis of psychotic disorders show inadequate reliability validity as for example indicated by significant differences in the diagnoses of DSM-III-R, DSM-IV, ICD-8, ICD-9, and ICD-10 classifications[16,17]. There is considerable inter-departmental diagnostic variability in the ICD-8 and ICD-10 diagnosis[18] explaining that schizophrenia may be often overdiagnosed or underdiagnosed[17]. In addition, the DSM suffers from a poor demarcation of the clinical heterogeneity present in schizophrenia[4,19]. For example, using machine learning techniques we discovered that schizophrenia consists of qualitatively distinct categories (including deficit *vs* non-deficit schizophrenia)[20], indicating that schizophrenia biomarker research which does not take this distinction into account is bound to fail. Also, the DSM case definitions of mood disorders including major depressive disorder (MDD) lack reliability validity[21], with MDD taxonomies showing minimal agreement between psychiatrists[22]. Furthermore, there was limited or no unification and harmonization of the DSM case definitions[18]. All in all, these taxonomies lack reliability and validity and are therefore counterproductive for research purposes[3-5,16,23-25].

BIOLOGICAL, MOLECULAR AND COGNITIVE PSYCHIATRY

A more radical physicalism theory, namely eliminative materialism, has been outlined in the past decades, especially under the influence of Churchland[26]. This theory applied to psychiatry relies on neuroscience and aims to replace the "folk" psychology vocabulary and methods on a systematic level by material concepts, namely aberrations in brain functions and neurocircuitry. Biological psychiatry aims to explain mental illness in terms of biological aberrations in neuronal functions; molecular psychiatry explains mental illness based on molecular pathways including the effects of genes and intracellular networks; and cognitive psychiatry explains mental illness though effects of cognitive impairments and their neuronal substrates. Nevertheless, the biological, molecular and cognitive approaches turned out to be insufficient to delineate biomarker or cognitive tools that externally validate the case definitions.

Biological, molecular and cognitive psychiatry research generally uses the "gold standard" DSM/ICD case definitions of mood and psychotic disorders in top-down research[3,4,16]. These methods commonly enter diagnosis as explanatory variable in GLM analysis or analysis of variance to analyze alterations in causome (*e.g.*, early lifetime trauma), biomarker levels, brainome data, and cognitive probe scores. The latter are entered as the dependent variables even when causal reasoning shows that they should be employed as the explanatory variables in logistic regression or other machine learning techniques, including neural networks. Consequently, most biological and cognitive psychiatry research projects employ unreliable diagnostic classes applied in inadequate model assumptions and tested with inappropriate statistical tests[3-5]. Also, molecular psychiatry uses a similar approach when examining pathways and networks or when conducting studies which associate genetic markers with the DSM/ICD taxonomies. A newer method, namely the Research Diagnostic criteria (RDoC), developed by the NIH, tries to integrate genetic, neurodevelopmental, environmental factors, with social, regulatory, cognitive and social domains, with negative and positive valence[25]. However, also the RDoC is largely a top-down concept driven by ex-consensus commitments by experts.

Another critical point is that the entire hypostasis of eliminative materialism of biological, molecular, and cognitive psychiatry is a fragmented or *"patchy" reductionist* approach[27] whereby psychiatric diagnoses tend to be reduced to neuronal entities, genetic markers, plasma biomarkers, intracellular signaling molecules, or functional MRI responses to emotional tasks. What is missing is an integrated model with precise mapping of genomics data, specific (causal and protective) and generalized (*e.g.*, context centered and lifestyle) environmental factors, and phenome features. All in all, the current "gold standard" DSM/ICD taxonomies are unreliable constructs and preclude using a deductive reasoning approach and, therefore, it is not surprising that biological, molecular, and cognitive psychiatry research was unable to revise the conventional classifications and did not provide valid predictions from a therapeutic perspective.

PAN-OMICS AND PRECISION PSYCHIATRY

Pan-omics psychiatry proposes to use systems biomedicine to decipher the complex non-linear interactions between pathways and intracellular networks that govern those pathways, and the multifactorial factors including genes and environmental factors that may trigger those pathways/networks[28]. Pan-omics psychiatry proposes to use a data-driven bottom-up approach to compute biosignatures consisting of molecular pathways and networks and symptoms as well as environmental features thereby developing pathway-phenotypes[28,29]. A related field is precision psychiatry, which is based on precision medicine defined as "an emerging approach for treatment and prevention that takes into account each person's variability in genes, environment, and lifestyle"[30]. Precision psychiatry aims to transform the psychiatric landscape through a bottom-up approach applied to pan-omics using system biology and computer science to compute a biosignature, which in turn may be used in a top-down approach to help to understand domains, which differ from components but allow to construct endophenotypes[31]. Both pan-omics and precision psychiatry propose to combine cognitive neuroscience, neural circuits, big data, molecular biosignatures, individual characteristics, physiology, and environment into a biosignature, which is a feature set defining an endophenotype[28,31]. These methods[31], however, do not aim to integrate all features of complex psychiatric disorders into a model characterized by causal paths linking causome (all possible causal factors), protectome (all possible protective factors), adverse output pathways (AOPs, namely biological, molecular, pan-omics, brain imaging features) and phenome (cognitome, symptomatome and phenomenome) feature sets.

BUILDING BLOCKS OF AN INTEGRATED MODEL

Figure 1 shows a causal theoretical model applicable to mood and psychotic disorders[3-7]. Causal reasoning based on state-of-the-art knowledge of these mental disorders indicates that causome features including genes and its products including enzymatic activity as well as specific environmentome factors (*e.g.*, early lifetime trauma) predict AOPs and the phenome of the illness[32]. Moreover, the generalized environmentome (including lifestyle, nutrition, toxins, context centered social, cultural, and political factors) should be added. Pan-omics may be employed to measure causome (genomics) and AOPs (*e.g.*, immunomics, epigenomics, transcriptomics, metabolomics, and proteomics). In psychiatry, another important AOP component is the brainome, which may be assessed using in vivo histology spectroscopy and magnetic resonance imaging. Also, the phenome of psychiatric disorders is very complex and consists of various feature sets including (1) staging of the disorder, as defined by recurrence of episodes and suicidal attempts, chronicity, *etc*.[32]; (2) the cognitome, namely the aggregate of cognitive features of the illness including in memory, executive functions, and attention; (3) the symptomatome, namely the aggregate of observed clinical symptoms, illness severity, subtypes, treatment responsivity; and (4) the phenomenome, namely the illness features as experienced by the patient[3,4].

One of the aims of our new nomothetic network psychiatry (NNP) approach is to reunify such data (1, 2, 3 and 4) into an illness model, which integrates different approaches including etiological, biological, molecular, pan-omics, cognitive, descriptive and phenomenological psychiatry, as well as folk psychology and postpsychiatry. In fact, machine learning conducted on these data will extract and select the most important features in a process referred to as feature re-engineering, selection, and learning to make the most accurate models of mood and psychotic disorders.

THE PRE-SPECIFIED CAUSAL FRAMEWORK

Figure 2 shows a framework or general structure which is based on scientific evidence linking a multitude of causome, protectome, AOPs, cognitome, brainome, staging, symptomatome, and phenomenome data. The selection of variables (indicators) and the concept of the framework are guided by the available theoretical knowledge, expertise, and information accumulated over the past decades and by formal causal reasoning. Nevertheless, the framework shown in Figure 2 is far for complete as for example socio-demographic data and generalized environmentome factors (*e.g.*, those

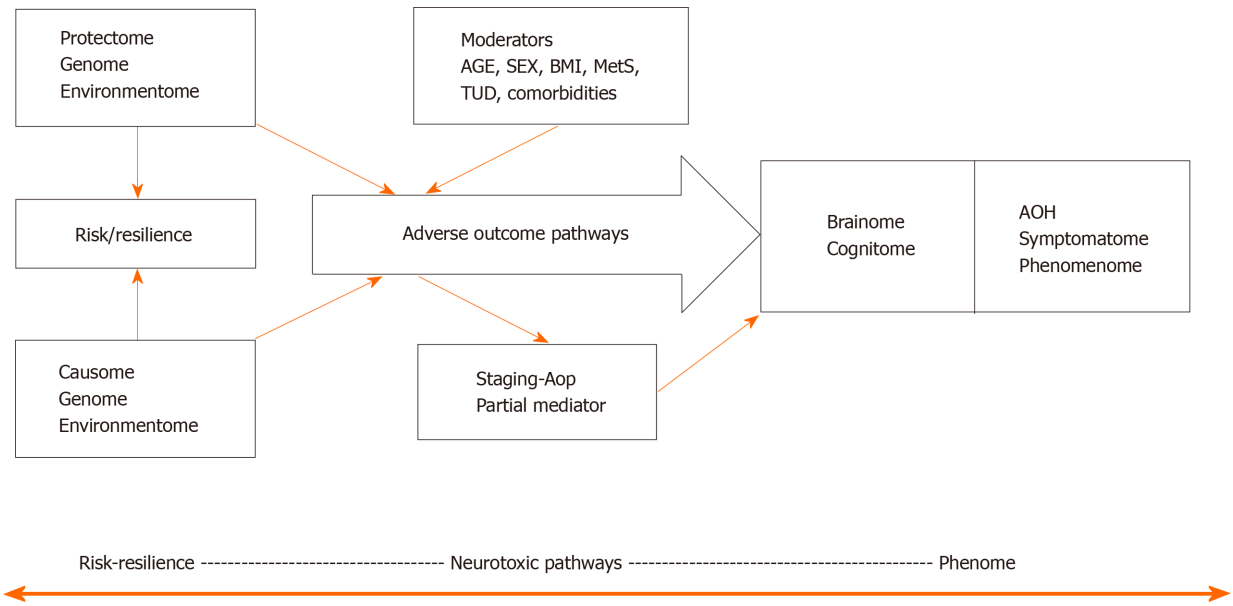


Figure 1 A causal theoretical model applicable to mood and psychotic disorders. This model links causome features (genes and gene products and environmentome factors) with adverse outcome pathways (AOP) and the phenome of the illness. The phenome consists of brainome and cognitome factors and adverse health outcomes including in the symptomatome and the phenomenome. Moreover, staging of illness may partly mediate the effects of risk/resilience and AOPs on the phenome. Age, sex, body mass index, metabolic syndrome, tobacco use disorder, and psychiatric and medical comorbidities are frequent moderators of the effects of R/R and AOPs on the phenome. AOP: Adverse outcome pathway; AOH: Adverse health outcome; MetS: Metabolic syndrome; BMI: Body mass index.

relevant to postpsychiatry) should be added to the model but are deleted from the figure for reasons of clarity. Consequently, data (facts) are accumulated to test this theoretical framework[33].

The multitude of data to be entered should first be reduced (dimensionality reduction) to a smaller number of relevant feature sets or vectors using feature construction processes[3,4]. The first step is to re-engineer the causome and protectome data into one of more new feature sets reflecting risk-resilience (R/R), namely the balance between causal and risk factors[3,4]. These R/R feature sets can consequently be used as input variables (predictors) in logistic models, regression analysis, and neural networks to expose their effects on the downstream features of the framework (AOP and phenome data). For example, in schizophrenia, we established that R/R indices re-engineered from genome data, *i.e.*, paraoxonase 1 (PON1) Q192R genotype combined with PON1 enzymatic activity, zonulin levels (a product of the haptoglobin 2-2 genotype), and lowered natural IgM (a protectome factor) predict AOPs (neuro-immune and neuro-oxidative toxicity pathways), cognitome (episodic and semantic memory and executive functions), symptomatome (psychosis, hostility, excitation, mannerism, negative symptoms) and phenomenome (self-rated quality of life) features[4]. In mood disorders, a new R/R index consisting of the PON1 Q192R genotype combined with PON1 enzymatic activity and early lifetime trauma predicts AOPs (antioxidant defenses and neuro-oxidative stress biomarkers), the symptomatome (depression severity, suicidal ideation, and mood disorders subtypes such as treatment resistance and melancholia) and the phenomenome (self-rated quality of life and disabilities)[3].

In the framework displayed in Figure 2, the newly re-engineered R/R feature sets are entered as input variables and can predict downstream feature sets as delineated through formal causal reasoning. The indicators of all downstream concepts are represented as latent vectors extracted from a set of features in reflective models because the aim is to construct a single underlying trait (*e.g.*, the symptomatome) which explains its manifestations (*e.g.*, all different symptom domains and phenotypes)[3-7]. The phenome feature sets are entered as output variables, whereas AOPs, cognitomone, and brainome feature sets predict the phenome and are predicted by the R/R features. It should be underscored that this method allows to reduce many features into a few relevant single traits. As such, the framework displayed in Figure 2 comprises one dependent variable (namely a latent vector reflecting the phenomenome) which is predicted by seven input variables, namely the RR, AOP, brainome, and symptomatome latent vectors. This parsimonious formal causal framework can then be trained, tested and validated using PLS structural equation

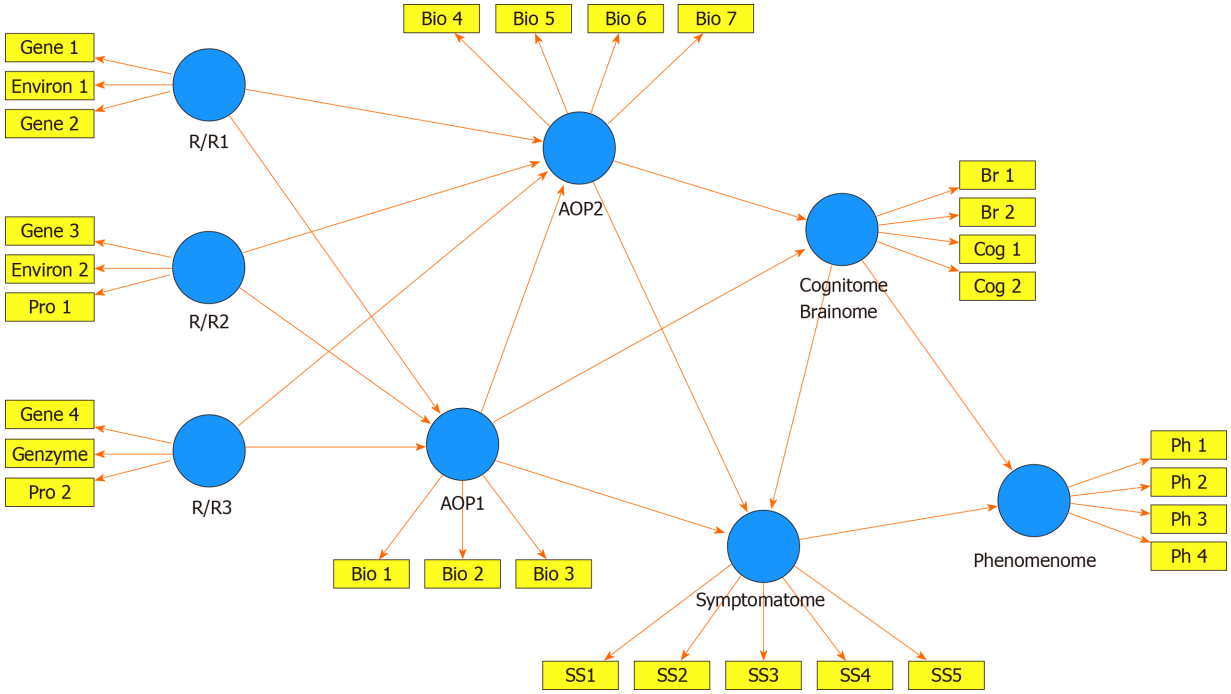


Figure 2 A causal framework of mental illness. This framework links a multitude of risk/resilience (R/R) features, with adverse outcome pathways (AOPs), the cognitome and brainome, the symptomatome, and phenomenome of mood disorders and schizophrenia. The R/R features are computed as a combination of causal and protective (Pro) genetic and environmental (Environ) features. The AOP feature sets are latent vectors (in reflective models) extracted from molecular or biological pathways/networks (Bio). The cognitome-brainome feature set is a latent vector extracted from cognitive test probe scores (Cog) and brain imaging (Br) scores. The symptomatome is entered as a latent vector extracted from symptom profiles, staging, and phenotypes (SS). The phenomenome is entered as a latent vector extracted from phenomenological data. R/R: Risk/resilience; AOP: Adverse outcome pathway; Pro: Protective; Bio: Biological; SS: Symptom profiles, staging, and phenotypes; Br: Brain imaging; Cog: Cognitive test probe scores.

modeling[3-7,34].

FROM A CAUSAL FRAMEWORK TO A CAUSALLY MODELED NOMOTHETIC NETWORK

PLS analysis allows to build pathway-phenotypes or biosignatures and train and evaluate a novel nomothetic model based on a combination of factor and regression analysis. Pathway-phenotypes may be exposed by combining for example AOPs with cognitome features into new reflective indicators of molecular paths and cognitive functions that underpin the illness[35]. Causal-pathway-phenotypes may be exposed by combining causome (*e.g.*, number of transfusions in transfusion-dependent thalassemia or TDT), AOPs (iron overload biomarkers and neuro-immune pathways as a consequence of the transfusions) with the phenome (depressive symptoms) into reflective indicators of a single latent trait, namely "depression due to immune activation as a consequence of transfusions and iron overload in TDT"[7]. Interestingly, in mood disorders, but not schizophrenia, symptomatome and phenomenome features may be combined as reflective manifestations of a single latent trait, namely the clinical – phenomenological phenome[3,4].

Figure 3 shows that the theoretical framework including new pathway-phenotypes can be trained and tested employing PLS on bootstrapped samples (*e.g.*, 5.000)[36]. Goodness of fit should be assessed using standardized root mean square residuals to avoid model misspecifications. The validity reliability of the latent vectors should be evaluated using psychometric properties such as composite reliability, rho-A, Cronbach's alpha, and average variance extracted values. All indicators of the LVs should show adequate loadings > 0.5 or by preference > 0.66[36]. Moreover, confirmatory tetrad analysis (CTA) should be used to ascertain whether the LV models are not mis-specified as reflective models, and blindfolding is used to test the construct cross-validated redundancies, which test the predictive relevance of the output LVs in the model[3,4]. Sample size determination and statistical power estimation should be performed based on (1) the psychometric properties of the vectors (factor loadings)

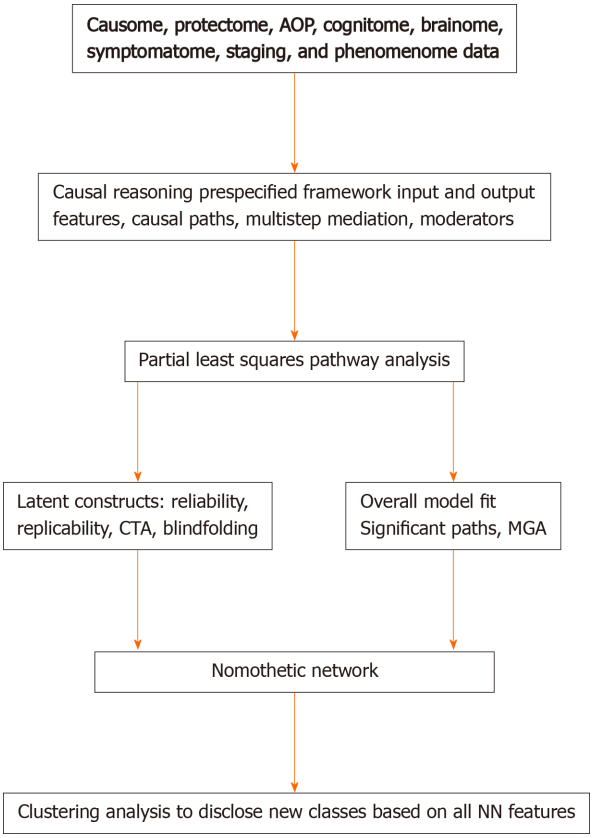


Figure 3 Nomothetic Network Psychiatry. Use of Partial Least Squares analysis to construct nomothetic networks (NN). Clustering techniques are conducted on the latent variable scores to expose new diagnostic classes. PLS: Partial Least Squares; NN: Nomothetic networks; AOP: Adverse outcome pathways; CTA: Confirmatory tetrad analysis; MGA: Multi-group analysis.

and the strength of the intercorrelations among the vectors, (2) the explained variance and the maximum number of arrows pointing to a construct, or (3) power analysis specific to multiple regression analysis[37,38]. These methods show that to achieve a power of 0.8 in the PLS model displayed in Maes *et al*[3] a relatively small sample size of n = 70-127 is sufficient. Nevertheless, larger sample sizes will yield more stable parameter estimates.

Consequently, PLS is conducted on bootstrapped samples which expose the path coefficients with exact p-values of all significant links (paths), as well as the total direct and indirect and specific indirect effects. Importantly, the indirect effects indicate the mediating effects of upstream on downstream indicators including in multistep mediating models. For example, in Figure 2, the R/R feature sets may have significant indirect effects on the phenomenome, which are mediated by the paths from AOP1 to the symptomatome or by the path from AOP2 to the cognitome to the symptomatome. In addition, also moderator (interaction) effects between 2 or more downstream indicators on upstream indicators may be added to the model which may account for possible moderating effects of age, sex, metabolic syndrome, and comorbidities. Finally, PLS allows to establish possible group differences in the model or paths using Multi-Group-Analysis (PLS-MGA) or permutations, which can be employed to examine differences in the model or paths, for example between different genotypes and between men and women. The latter is important to examine in schizophrenia and mood disorders because sexual dimorphisms were detected in those disorders[39,40]. Using PLS-MGA in schizophrenia we found significant differences between both women and men in the path from AOP to the phenomenome (quality of life) with a significant impact in women, but not in men[4]. On the other hand, no significant sex-related differences in the nomothetic network or in any of the pathways could be detected in mood disorders[3,5].

THE NOMOTHETIC MODEL AND THE REIFICATION OF DESCRIPTIVE ILLNESS NARRATIVES

In summary, a bottom-up, data-driven model of mood disorders and schizophrenia may be constructed using the knowledge-based causal framework shown in Figure 2 and by assembling R/R, AOPs, and phenome feature sets into an explicit data model, namely the PLS nomothetic network. Nomothetic indicates the tendency to generalize and to derive models ("laws") from independent variables, which explain variations in phenomena[41]. As such, the nomothetic network approach objectivates the symptomatome and phenomenome of mood disorders and schizophrenia[3-5], and, therefore, translates R/R, AOP, brainome, and cognitome feature sets into relevant descriptive narratives. The process which reifies the abstract concepts of descriptive narratives to realize a more concrete and material concept using computer science is named "reification of clinical diagnosis". It is important to note that in contrast to pan-omics and precision psychiatry, the aim of our nomothetic network approach is not only to compute pathways-phenotypes or biosignatures, but especially to make a nomothetic network, with causal links between the building blocks of the disease.

It should be added that this nomothetic network approach, in contrast to biological psychiatry models[42-44], may pass Karl Popper's critical rationalism test[33]. Indeed, our nomothetic networks are progressive (the model is based on all available knowledge), parsimonious (through feature reduction), changeable (other researchers can elaborate on the model and add more indicators or delete less robust features), provisional (the latent variable scores of the network will change when more pan-omics and brainome data are added), and falsifiable (the network can be refuted or corroborated). In this respect, our nomothetic networks deserve validation in more heterogeneous study groups consisting of individuals with comorbid psychiatric and medical disorders.

DISCOVERY OF NEW CLASSIFICATIONS BASED ON THE FEATURE SET SCORES

After integrating the validated feature vectors into a well-fitting nomothetic network, latent variable scores may be computed which reflect the severity of the various R/R, AOP, brainome, cognitome, staging, symptomatome, and phenomenome feature sets. The latter may be employed in unsupervised pattern recognition methods, including clustering analysis, to expose new categories (Figure 3). Previously, we employed different clustering techniques on such latent variable scores including K-mean, K-median, and Ward's and Forgy's methods[3-5]. Figure 4 shows a hypothetical example of cluster analysis-generated classes, with the latent variable scores (in z transformation) displayed in a clustered bar graph. This figure shows a normal cluster with healthy control subjects and two patients clusters. The second patient cluster may be discriminated from the first cluster (and from controls) by higher R/R, AOP, cognitive and brainome, symptomatome and phenomenome scores. The first patient cluster may be discriminated from controls by increased R/R3, AOP, and phenome scores. Previously, we showed that, in mood disorders, these new bottom-up cluster analysis-derived classes are more influential for classification purposes than the top-down classification into bipolar type 1 and type 2 and major depression. As such, new mechanistic, biosignature-based, and/or transdiagnostic classes may be discovered[3,5].

Nevertheless, these new classes should be cross-validated in independent samples using other machine learning methods including support vector machine with 10-fold cross-validation or soft independent modeling of class analogy (SIMCA)[7]. It is interesting to note that our nomothetic networks computed in mood disorders and schizophrenia contain self-rated phenomenological features (including self-rated quality of life and severity of disabilities), and, therefore, may comprise idiographic features[3,4]. Therefore, the latent variable scores not only delineate an objective nomothetic network and new diagnostic classes, but also shape an idiomatic feature profile, which is unique for every individual. As such, adequate treatments of mood disorders and schizophrenia should target the components of the nomothetic networks (R/R, AOP, brainome) constructed in those disorders. In addition, the individualized feature profile allows a more personalized treatment targeting aberrations in specific R/R, AOP, cognitome, brainome, and staging latent variable scores.

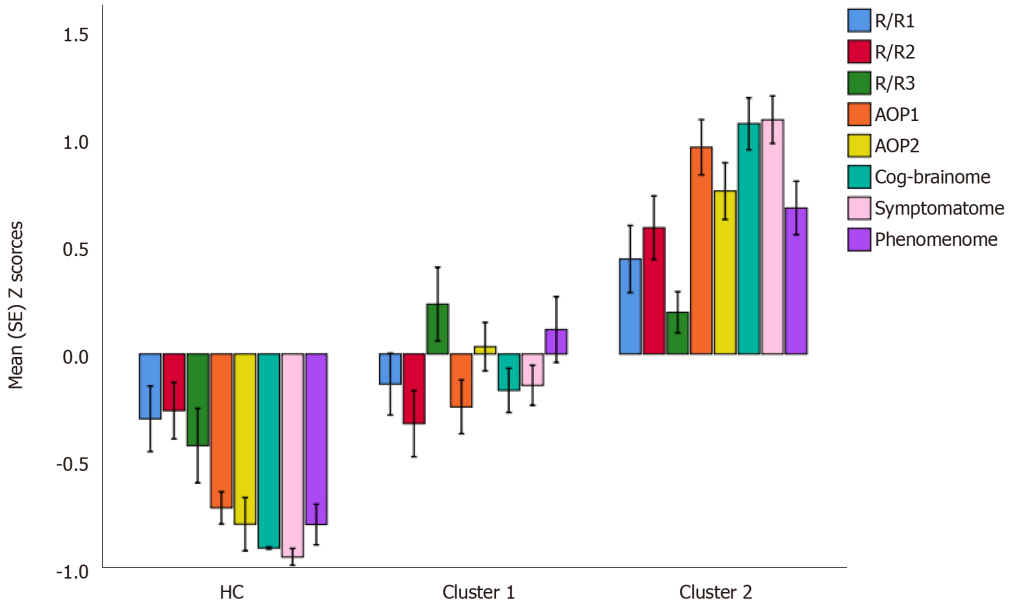


Figure 4 A hypothetical example of cluster analysis-generated classes, with the latent variable scores (in *z* transformation) displayed in a clustered bar graph. R/R: Risk/resilience; AOP: Adverse outcome pathway; HC: Healthy control.

CONCLUSION

In this paper we explained how to use the new nomothetic network psychiatry (NNP) approach to construct new causal models of mental illness by machine learning techniques, which assemble all features of mental illness, namely risk-resilience, AOPs, cognitome, brainome, symptomatome, staging, and phenomenome scores. PLS analysis may successfully be used to train, test and validate those models, to build pathway-phenotypes or biosignatures, and to construct comprehensive models of mood disorders and schizophrenia which objectivate the clinical phenome of those disorders. Clustering analysis performed on all illness features reduced into latent traits may expose relevant new (transdiagnostic) classes. The reification of the clinical diagnosis of mood disorders and schizophrenia (and by inference other psychiatric disorders) using the nomothetic network psychiatry approach is an awaited achievement which constitutes a major paradigm shift in psychiatry[16].

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 January 19; 11(1): 13-26

DOI: 10.5498/wjp.v11.i1.13

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

What gets in the way of social engagement in schizophrenia?

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Author contributions: Mote J, Campellone TR, and Kring AM were involved in the conception of the study; Weittenhiller LP, Mikhail ME, and Kring AM contributed to the study design and coding manual development; Weittenhiller LP and Mikhail ME conducted didactic trainings and managed coding implementation; Weittenhiller LP performed the analyses and wrote the initial drafts of the manuscript with significant contributions made by Kring AM; all authors edited and approved the final version of the manuscript.

Supported by National Science Foundation Graduate Research Fellowship Program, No. 1752814.

Institutional review board statement: The study was approved by the University of California, Berkeley Institutional Review Board.

Informed consent statement: All study participants provided informed written consent.

Conflict-of-interest statement:

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Abstract

BACKGROUND

Social engagement-important for health and well-being-can be difficult for people with schizophrenia. Past research indicates that despite expressing interest in social interactions, people with schizophrenia report spending less time with others and feeling lonely. Social motivations and barriers may play an important role for understanding social engagement in schizophrenia.

AIM

To investigate how people with schizophrenia describe factors that impede and promote social engagement.

METHODS

We interviewed a community sample of people with (n = 35) and without (n = 27) schizophrenia or schizoaffective disorder about their social interactions with friends and family over the past week and planned social activities for the coming week. We reviewed the interview transcripts and developed a novel coding system to capture whether interactions occurred, who had initiated the contact, and frequency of reported social barriers (*i.e.*, internal, conflict-based, logistical) and social motivations (*i.e.*, instrumental, affiliative, obligation-based). We also assessed symptoms and functioning.

RESULTS

People with schizophrenia were less likely than people without schizophrenia to have spent time with friends [t (51.04) = 2.09, P = 0.042, d = 0.51)], but not family. People with schizophrenia reported more social barriers than people without schizophrenia [F (1, 60) = 10.55, P = 0.002, ηp2 = 0.15)] but did not differ in

None declared.

Data sharing statement: Data available on request from the corresponding author at lauren.weittenhiller@berkeley.edu.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Manuscript source: Unsolicited manuscript

Specialty type: Psychology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: October 23, 2020
Peer-review started: October 23, 2020
First decision: December 4, 2020
Revised: December 16, 2020
Accepted: December 27, 2020
Article in press: December 27, 2020
Published online: January 19, 2021

P-Reviewer: Khan MM
S-Editor: Zhang L
L-Editor: A
P-Editor: Li JH

reported social motivations. Specifically, people with schizophrenia reported more internal [t (45.75) = 3.40, P = 0.001, d = 0.83)] and conflict-based [t (40.11) = 3.03, P = 0.004, d = 0.73)] barriers than people without schizophrenia. Social barriers and motivations were related to real-world social functioning for people with schizophrenia, such that more barriers were associated with more difficulty in close relationships (r = -0.37, P = 0.027) and more motivations were associated with better community functioning (r = 0.38, P = 0.024).

CONCLUSION
These findings highlight the importance of assessing first person accounts of social barriers and motivations to better understand social engagement in schizophrenia.

Key Words: Social engagement; Schizophrenia; Social motivation; Social barriers

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Core Tip: We examined factors that may impede and promote social engagement in schizophrenia. We coded social barriers and motivations from transcribed negative symptoms interviews. We found that barriers, such as conflicts with other people or negative beliefs about the self, were prominent in schizophrenia. Interestingly, when explicitly prompted, people with schizophrenia reported interest in and motivation for social interactions. Nevertheless, social barriers may get in the way of them following through.

Citation: Weittenhiller LP, Mikhail ME, Mote J, Campellone TR, Kring AM. What gets in the way of social engagement in schizophrenia? *World J Psychiatr* 2021; 11(1): 13-26
URL: https://www.wjgnet.com/2220-3206/full/v11/i1/13.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i1.13

INTRODUCTION

Social engagement is a central part of life and is linked to many benefits, such as wellbeing, health, and longevity[1]. Unfortunately, limited social engagement is common in schizophrenia[2] and people with schizophrenia often miss out on the benefits of such engagement. In this study, we sought to determine contributing factors to limited social engagement in schizophrenia. Specifically, we examined how people with and without schizophrenia talk about their social engagement with friends and family to better understand factors that motivate such engagement and barriers that might get in the way.

Why might people with schizophrenia engage in fewer social interactions? Limited social engagement may be indicative of social disinterest[3]. Indeed, people with schizophrenia report spending less time around others and set fewer social goals compared to people without schizophrenia[4-6]. However, other evidence indicates that people with schizophrenia describe social relationships as equally important[7,8] and express as much interest in social activity compared to people without schizophrenia[4,9]. Moreover, people with schizophrenia report a similar or even greater preference to be with others as those without schizophrenia when they find themselves alone[10,11]. People with schizophrenia also express more social interest than those with other psychiatric illnesses[12]. Even as people with schizophrenia profess an interest in social interactions, they also report feeling lonely[5,13-15], suggesting they have social needs that are not being met. Insofar as diminished interest does not fully account for limited social engagement in schizophrenia, we sought to examine other possible barriers. Understanding what might get in the way of social engagement in schizophrenia can be an important first step toward helping people with schizophrenia obtain the myriad benefits of social interactions.

Social barriers

Barriers that may interfere with social engagement in schizophrenia include internal

states, conflicts with others, or logistical factors. Prior research has identified several possible internal barriers in schizophrenia, including low self-esteem, internalized stigma, and defeatist performance beliefs[16-19]. Symptoms may also interfere with social engagement: Greater positive symptoms are associated with lower relationship satisfaction[20], and greater negative symptoms are associated with smaller social network sizes[21,22].

Conflicts with others, whether in the form of disagreements, social discrimination, or stigma-related rejection, may also interfere with social engagement. For example, families with a person with schizophrenia report more frequent arguments and heightened tension than other families[23]. People with schizophrenia are often reluctant to disclose their illness to friends, fearing that once they do, they will be rejected[24].

Logistical barriers, such as limited financial means, may also get in the way of social engagement. People with schizophrenia are more likely to be unemployed[25], which could restrict social network size and variety[26]. Social activities that require money or transportation may also be less accessible[27].

Social motivations

Considering what motivates people to form and maintain relationships is also important for understanding social engagement. Some motivations for relationships are instrumental, arising from a desire for social activity to acquire tangible benefits[28,29]. In this way, relationships are a means to an end. As caregivers of people with schizophrenia are at times responsible for meeting various needs of their loved ones[30], the desire for assistance may be a motivation for social engagement.

Alternatively, social relationships can be motivating in and of themselves[29,31]. Affiliative motivations focus on companionship, mutual care, and the exchange of emotions as drivers of engagement with others. People with schizophrenia report wanting social relationships and even consider them a primary source of meaning[32], suggesting that affiliative motivations are an important aspect of social engagement. Another type of social motivation is obligation-based, which refers to the desire to meet personally or societally determined standards of appropriate social behavior[33], or how a person "should" behave. Because it is considered normative to have relationships, people with schizophrenia report this as an important indication of health[34].

The importance of first-person accounts

How people with schizophrenia describe their social experiences can offer a window into social barriers and motivations and provide an important perspective for understanding social engagement. Of the few studies in schizophrenia that have used such an approach, most have focused on lexical characteristics of speech, linguistic abnormalities, word counts, or speech coherence and appropriateness[35-40]. A notable exception is the work of Lysaker *et al*[41], who assessed social worth, social closeness, and personal agency in spoken narratives of people with schizophrenia. The more frequently people with schizophrenia referred to these social themes in their narratives, the better their social functioning.

Present study

We sought to answer four questions about social engagement in schizophrenia. First, we asked whether people with and without schizophrenia differed in the frequency and initiation of interactions with family and friends in the past week. Second, we asked whether people with and without schizophrenia differed in reported types of social barriers and motivations. Third, we asked whether social barriers and motivations differed by relationship type (friends, family). Fourth, we asked whether social barriers and motivations were related to functioning and symptoms for people with schizophrenia.

MATERIALS AND METHODS

Participants

Thirty-five people with schizophrenia (n = 26) or schizoaffective disorder (n = 9) and 27 people without a schizophrenia spectrum disorder participated. People with schizophrenia and schizoaffective disorder did not differ from one another on any demographic, clinical, or coded variable; we collapsed across these groups for

analyses. Participants were recruited from board and care homes, nonprofit agencies, and Craigslist and were part of the multi-site study that developed the Clinical Assessment Interview for Negative Symptoms[42]. The data presented here do not overlap with that study.

Diagnoses were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P)[43]. For controls, we administered the SCID non-patient version (SCID-I/NP)[44] to confirm absence of schizophrenia spectrum disorders. Any participant with a history of head injury or neurological disorder, a current mood episode, or substance use disorder within the past six months was not invited to participate. All participants provided written informed consent. As shown in Table 1, the groups did not differ in age, sex, race, marital status, education, or estimated intelligence quotient (measured by the Wechsler Test of Adult Reading[45]).

Measures

Clinical Assessment Interview for Negative Symptoms beta version: Trained raters administered the beta version of the Clinical Assessment Interview for Negative Symptoms (CAINS), and the interviews were videotaped. The CAINS includes several manualized open-ended probes for each item with additional questions asked as needed for clarity. The CAINS-beta differs from the final CAINS[46] in length (16 rather than 13 items) and in the inclusion of separate questions about romantic relationships.

We examined responses to the first five items of the CAINS-beta. The first three items assessed social motivation and enjoyment in (1) family; (2) romantic relationships; and (3) friendships. Participants were asked to describe their social interactions over the preceding week (*e.g.*, Have you been motivated to be around or in touch with your family/partner/friends in the past week?). The fourth item asked participants to describe pleasure experienced in past week social activities (*e.g.*, Did you have any enjoyable interactions with other people?), and the fifth item asked about expected pleasure from social activities over the next week (*e.g.*, What do you think you will enjoy doing in the next week with other people?).

Interview coding: Interviews were transcribed and coded by trained research assistants. We developed a coding manual containing definitions and examples for all variables, and four raters, blind to diagnostic status, did the coding. A different rater reviewed all data for entry accuracy and coding manual adherence.

Mirroring the final CAINS[46], marital relationships were included with family items, and dating relationships were included with friend items. For friends and family, coders rated "whether any interaction had occurred" over the past week—including phone calls, text messages, e-mails, or in-person contact—dichotomously (present, absent). When an interaction was reported, "initiation" was coded on a 3-point scale: (1) Social partner(s) initiated all interactions; (2) Participant initiated some and social partner initiated some; and (3) Participant initiated all interactions.

Coders determined which type of social barrier or motivation a statement referred to and then computed the total number of social barriers and motivations of each type. Social barriers were defined as causing an interaction to be cut short or to not occur at all. Coders counted the frequencies of three types of barriers. Internal barriers included psychological states and beliefs that prevented interaction, including negative self-perceptions or self-stigma (*e.g.*, "No one would want to be my friend"), psychiatric symptoms, negative beliefs about social interactions (*e.g.*, "People just let you down"), and having goals or priorities that took precedence over social interaction (*e.g.*, "I want to finish my degree before I look for a relationship"). Conflict-based barriers included discrimination (*e.g.*, "My parents disowned me because I'm gay"), rejection (*e.g.*, "She said she didn't want to date anymore"), and social conflict (*e.g.*, "All we ever do is fight"). Logistical barriers referred to geographic distance, lack of time, mismatched schedules, non-psychiatric illness, lack of financial resources, or perceived lack of access to an appropriate social partner.

Coders also computed the frequencies of three types of social motivations. Instrumental motivations included tangible benefits (*e.g.*, a relative paying for rent) and perceived benefits to a participant's physical or mental wellbeing or personal development (*e.g.*, "She keeps me sane"). Affiliative motivations included positive attributes of interaction partners (*e.g.*, "He's funny"), social support, acceptance of self (*e.g.*, "I feel like I can be myself around them"), physical intimacy, and avoidance of loneliness and social isolation. Obligation-based motivations included a desire to provide something to an interaction partner (*e.g.*, "I want to be a positive role model for my sister"), or expectations of normative behavior (*e.g.*, "I called my friend on her birthday because it is the polite thing to do"). Finally, we counted the total number of words participants uttered using the Linguistic Inquiry and Word Count program[47].

Table 1 Demographic and clinical characteristics

	Schizophrenia	Control
Age (in year)	45.20 (10.96)	45.11 (8.51)
Sex, *n* (%)	12 Female (34.3)	10 Female (37.0)
Race, *n* (%)		
White	18 (51.4)	8 (29.6)
Black	9 (25.7)	10 (37.0)
Asian	2 (5.7)	3 (11.1)
Pacific Islander	1 (2.9)	0 (0)
Multiracial	2 (5.7)	15 (8.5)
Ethnicity: Hispanic/Latino, *n* (%)	3 (8.6)	4 (14.8)
Education (in year)	14.32 (2.80)	14.96 (2.79)
Employed, *n* (%)	16 (45.7)	15 (55.6)
Marital status		
Married	14.3%	29.6%
Widowed	2.9%	0%
Divorced/Separated	17.1%	22.2%
Never married	65.7%	44.4%
Unknown	0%	3.7%
Percent employed	45.7%	55.6%
WTAR	104.12 (15.18)	102.67 (12.45)
Diagnosis	Schizophrenia: 74.3%	--
	Schizoaffective: 25.7%	
Duration of illness (in year)	22.52 (12.42)	--
BPRS	46.03 (11.81)	--
RFS		
Working productivity	4.43 (2.12)	--
Independent living skills	5.37 (1.57)	--
Immediate social network	5.20 (1.62)	--
Extended social network	4.37 (1.94)	--
CAINS-EXP	1.21 (0.82)	0.56 (0.59)
CAINS-MAP[a]	1.87 (0.71)	1.00 (0.68)

Values are means with standard deviations in parentheses or numbers with percentages.
[a]Mean of 13 items from the final Clinical Assessment Interview for Negative Symptoms and romantic relationship motivation item from Clinical Assessment Interview for Negative Symptoms-beta. BPRS: Brief Psychiatric Rating Scale; CAINS-EXP: Clinical Assessment Interview for Negative Symptoms, Expression Subscale; CAINS-MAP: Clinical Assessment Interview for Negative Symptoms, Motivation and Pleasure Subscale; RFS: Role Functioning Scale; WTAR: Wechsler Test of Adult Reading.

Clinical ratings: We measured functioning using the Role Functioning Scale[48] with its 1 (minimal functioning) to 7 (optimal functioning) point scale. The Role Functioning Scale contains four subscales—working productivity, independent living and self-care, immediate social network relationships, and extended social network relationships. We assessed symptoms using a 24-item version of the Brief Psychiatric Rating Scale rated on a 7-point scale[49].

Data analyses

We conducted independent samples *t*-tests and chi-square tests to compare demographics, word count, contact, and initiation. For barriers and motivations, we conducted 2 Group (schizophrenia, control) X 2 Relationship Type (family, friends) X 3 Barrier (internal, logistical, conflict-based) or Motivation Type (instrumental, affiliative, obligation-based) mixed effect analyses of variance. Sphericity violations were Greenhouse-Geisser corrected; effect sizes are reported as Cohen's d and partial eta squared (ηp2). We computed Pearson correlations between barriers, motivations, functioning, and symptoms within the schizophrenia group.

RESULTS

Preliminary analyses

Two coders rated a third of interviews (equal numbers of people with and without schizophrenia) to assess inter-rater agreement. Coders achieved a high rate of agreement, with intraclass correlations[50] ranging from 0.83-1.00.

People with (M = 1652.66, SD = 958.25) and without (M = 1348.08, SD = 926.58) schizophrenia did not differ significantly in the amount of words spoken during the interview [t (59) = 1.25, P = 0.22, d = 0.32)]. Thus, any group differences in coded barriers and motivations were not a function of fewer words uttered by either group. We also found no significant differences between men and women for any variable, and thus we collapsed across sex for subsequent analyses.

Contact and initiation

Both groups were just as likely to have interacted with family over the past week, but people with schizophrenia were less likely to have interacted with friends compared to controls, [t (51.04) = 2.09, P = 0.042, d = 0.51]. People with schizophrenia were no more likely to be living with family than those without schizophrenia [t (59) = -0.96, P = 0.34, d = 0.25)], suggesting that greater ease of access did not contribute to rates of reported family interactions for the schizophrenia group. When interactions did occur, the groups were equally likely to have initiated interactions with family. However, people with schizophrenia were less likely to have initiated interactions with friends, [t (46) = 2.75, P = 0.008, d = 0.80].

Barriers

We found a significant group main effect [F (1, 60) = 10.55, P = 0.002, ηp2 = 0.15)], indicating that people with schizophrenia reported more barriers overall than people without schizophrenia (see Table 2). However, the Group X Barrier Type interaction was also significant [F (2, 120) = 3.27, P = 0.041, ηp2 = 0.05)], indicating that the group differences depended upon barrier type. As shown in Figure 1, people with schizophrenia reported more internal [t (45.75) = 3.40, P = 0.001, d = 0.83) and conflict-based barriers [t (40.11) = 3.03, P = 0.004, d = 0.73)] than people without schizophrenia; the groups did not differ in reported logistical barriers.

We also found a significant relationship type main effect [F (1, 60) = 10.35, P = 0.002, ηp2 = 0.15)], indicating that all participants reported more barriers for friends than family [t (61) = 3.36, P = 0.001, d = 0.43)]. However, this was qualified by a significant Relationship Type X Barrier Type interaction [F (2, 120) = 3.78, P = 0.026, ηp2 = 0.06)]. As shown in Table 3, whereas logistical and conflict-based barriers were similar across friends and family, all participants reported more internal barriers for friends than for family [t (61) = 4.10, P < 0.001, d = 0.52)].

Motivations

Neither the group main effect [F (1, 60) = 0.17, P = 0.68, ηp2 = 0.003)], nor the Group X Motivation Type interaction were significant [F (1, 60) = 1.92, P = 0.17, ηp2 = 0.03)]. However, the motivation type main effect was significant [F (1.10, 65.89) = 143.42, P < 0.001, ηp2 = 0.71)]; all participants reported more affiliative than instrumental [t (61) = 12.07, P < 0.001, d = 1.53)] or obligation-based [t (61) = 8.36, P < 0.001, d = 1.06)] motivations (see Table 2). In addition, participants reported more obligation-based than instrumental motivations [t (61) = 4.14, P < 0.001, d = 0.53)].

This finding was qualified by a significant Relationship Type X Motivation Type interaction [F (1.19, 71.41) = 4.14, P = 0.039, ηp2 = 0.07)]. Whereas obligation-based motivations were similar across friends and family, all participants reported more instrumental [t (61) = 2.02, P = 0.048, d = 0.26)] and affiliative motivations [t (61) = 2.14,

Table 2 Contact, initiation, barriers, and motivations by group

	Schizophrenia	Control	*P* value	Cohen's *d*
Contact	1.84 (0.23)	1.93 (0.18)	0.09	0.43
Initiation	1.75 (0.66)	2.03 (0.66)	0.11	0.42
Barriers				
Internal	2.00 (2.28)	0.57 (0.86)	0.001	0.83
Logistical	1.57 (1.26)	1.43 (1.46)	0.68	0.11
Conflict-based	1.53 (2.40)	0.24 (0.64)	0.004	0.73
Motivations				
Instrumental	0.90 (1.10)	0.69 (0.91)	0.41	0.21
Affiliative	8.27(5.67)	8.98 (4.15)	0.59	0.14
Obligation-based	3.09 (4.57)	3.39 (4.06)	0.79	0.07

Values are means with standard deviations in parentheses.

Table 3 Barriers and motivations by relationship status

	Friends	Family	*P* value	Cohen's *d*
Barriers				
Internal	1.09 (1.60)	0.29 (0.69)	0.001	0.52
Logistical	0.85 (1.02)	0.65 (0.91)	0.26	0.15
Conflict-based	0.52 (1.55)	0.44 (0.81)	0.68	0.05
Motivations				
Instrumental	0.51 (0.67)	0.30 (0.64)	0.048	0.26
Affiliative	4.82 (3.25)	3.76 (3.05)	0.037	0.28
Obligation-based	0.38 (0.66)	0.55 (0.78)	0.23	0.15

Values are means with standard deviations in parentheses.

$P = 0.037$, $d = 0.28$)] for friends than for family.

Correlations

As shown in Table 4, barriers and motivations were significantly associated with functioning. Internal and conflict-based barriers were moderately, negatively correlated with independent living skills, indicating that the more difficulties people with schizophrenia experienced with self-care, the greater the number of internal and conflict-based barriers they reported. More logistical barriers were associated with greater difficulties with close others. Motivations were moderately related to social functioning; in particular, more affiliative motivations were associated with significantly better social functioning within the broader community.

Interestingly, only conflict-based barriers were significantly related to total symptoms (but not negative or positive symptoms separately), suggesting that other types of barriers/motivations may be somewhat independent of symptom severity.

DISCUSSION

We investigated reported barriers to and motivations for social engagement in people with and without schizophrenia. Despite describing social engagement with the same number of words, people with schizophrenia reported more social barriers than those without schizophrenia, yet just as many social motivations. Importantly, social barriers and motivations were also related to functioning. Our findings suggest that particular

Table 4 Correlations with functioning and symptoms

	Barriers			Motivations		
	Internal	Logistical	Conflict-based	Instrumental	Affiliative	Obligation-based
Role Functioning Scale						
Working productivity	0.03	0.13	-0.20	-0.01	0.23	0.06
Independent living/self-care	-0.36[a]	0.02	-0.43[b]	-0.08	-0.26	-0.22
Immediate social network	-0.16	-0.37[a]	-0.18	-0.08	0.01	-0.16
Extended social network	-0.18	0.12	-0.20	-0.10	0.38[a]	0.22
BPRS	0.25	-0.14	0.50[b]	0.20	-0.03	-0.001

[a]$P < 0.05$.
[b]$P < 0.01$. BPRS: Brief Psychiatric Rating scale.

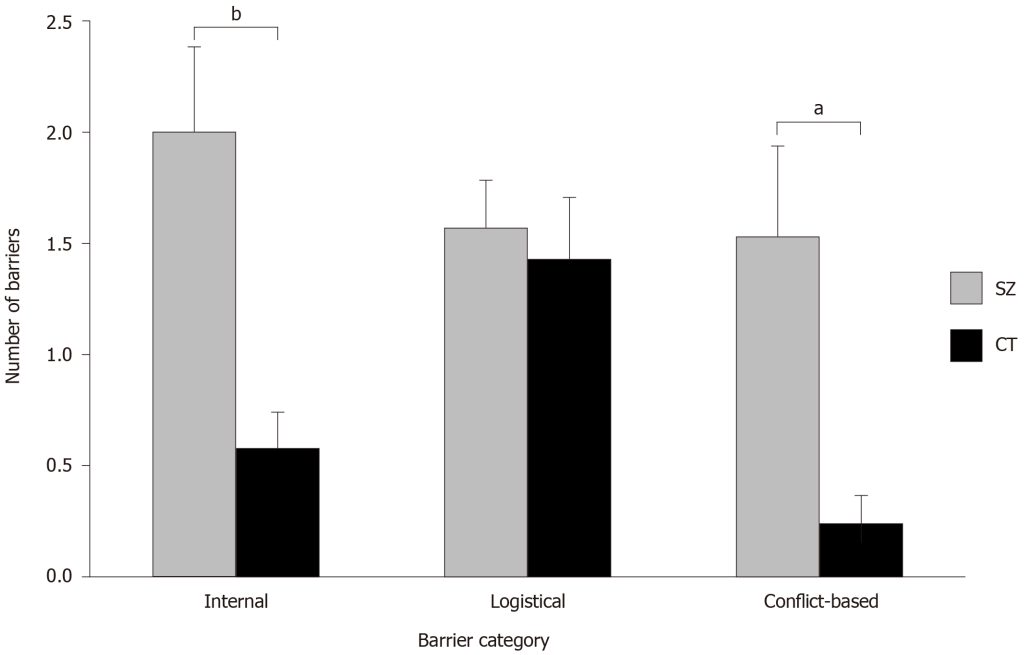


Figure 1 Barriers reported (collapsed across relationship type) for people with (SZ) and without (CT) schizophrenia. People with schizophrenia reported significantly more barriers than controls, in general, as well as more internal and conflict-based barriers specifically. [a]$P < 0.01$ and [b]$P < 0.001$. SZ: Schizophrenia; CT: Computed tomography.

types of social barriers and motivations may impede social engagement for people with schizophrenia and impact real-world social behavior, and they provide valuable information on directions for improving social engagement.

Consistent with previous research[51], we found that people with schizophrenia were less likely to have interacted with or initiated contact with friends over the past week compared to controls. However, we found no differences in contact or initiation with family. These findings are clinically important, as frequency of contact with friends is more predictive of clinical recovery than contact with family[52]. Moreover, evidence suggests that people with schizophrenia lose connections with close friends early in the course of illness[51], which may contribute to limited social engagement over the illness course[53].

Compared to controls, people with schizophrenia reported experiencing more internal barriers and conflict-based barriers. These findings are consistent with evidence that people with psychotic disorders feel less at ease and more threatened while in the company of others compared to people without psychotic disorders[11]. It is possible that people with schizophrenia are more sensitive to perceiving negativity in social encounters; however, it is also possible that negative attitudes are borne from actual social rejection.

Although speculative, conflict-based barriers may be associated with stigma-based rejection. Heightened discrimination and rejection that people with schizophrenia face may perpetuate negative beliefs about social interactions, resulting in a cycle of negative social experiences. It would be helpful for future work to explore the origins and bidirectional causality of conflicts involving people with schizophrenia. Impairments in social cognitive processes (*e.g.*, social cue perception, empathy), which we did not assess, could make resolving disagreements more challenging for people with schizophrenia[54]. Examining linkages between social barriers and stigma-based rejection is an important direction for future research.

Both groups reported more barriers to interactions with friends than with family, and this was particularly evident for internal barriers. Friendships are inherently more difficult since they are not "built in" and thus require more effort to establish and maintain. Family members may reach out frequently even if their loved one has negative beliefs about interactions. By contrast, friends may not put in this effort. Coupled with our finding that people with schizophrenia were less likely to interact with friends and also that barriers were more common for interactions with friends, it seems especially important to study friendships in future studies.

Interestingly, we found that people with schizophrenia reported being comparably motivated for friend and family interactions as people without schizophrenia. This finding may seem at odds with other studies indicating that people with schizophrenia have deficits in social motivation[55-57]. Two methodological differences may account for this discrepancy. First, similar to Gard *et al*[4], we asked people to report on their actual, "real-life" social interactions over the past week following several guided prompts. By contrast, laboratory studies of social motivation use tasks of simulated social interactions. Second, we coded actual behavior (*e.g.*, went to dinner with family) as well as articulated motives (*e.g.*, reported desire to see family). This approach differs from studies of effort expenditure[56,58] that focus on behavioral action. It will be informative in future studies to examine social motivations using a variety of approaches, such as ecological momentary assessment, passive mobile data collection, or virtual reality techniques[59]. Moreover, it will be essential to replicate this finding with a larger sample, as social motivation difficulties, like any deficit in schizophrenia, are not observed in all people with the diagnosis.

We found that both groups reported more affiliative and instrumental motivations for friendships than family relationships, which is noteworthy since people with schizophrenia were less likely to have had contact with friends. That is, people with schizophrenia reported being motivated to interact with friends for affiliative and instrumental reasons as much as controls, yet they were less likely to have done so over the past week. This finding highlights an important disconnect between reported interest and actual behavior for people with schizophrenia[59-61]. Although experiencing motivation for friendships may provide entry to important support that comes from friendships[62-65], receipt likely requires contact with friends. Understanding how internal or conflict-based social barriers can be reduced will likely help increase contact and benefits from friends.

We also found that barriers and motivations were associated with real-world functioning for people with schizophrenia. Because navigating the social world is important for autonomous living, conflict-based barriers, such as stigma and rejection, may make it more challenging for people with schizophrenia to maneuver bureaucratic systems or manage shopping or transportation. Similarly, internal barriers, like negative beliefs about the self, may be detrimental to the self-efficacy necessary to pursue independent living[66].

Encouragingly, we found no group differences in reported logistical barriers, perhaps because the groups did not differ in education or employment status. Nevertheless, for people with schizophrenia, logistical barriers were associated with functioning in close relationships. Although finances are but one type of logistical barrier, limited means can make it more difficult for people with schizophrenia to afford social activities or access transportation. Relatedly, unemployment[25] or lessened community integration[67] may make it challenging to get in touch with or visit other people.

The more that people with schizophrenia were motivated by the interpersonal aspects of relationships, the better their functioning in wider spheres of social contact such as clubs, churches, or social recreational activities. Perhaps people who value the relational aspects of social interactions seek out more opportunities for contact with members of their communities. Given the cross-sectional and correlational nature of our data, however, it is impossible to assess directionality. Nevertheless, social integration in different spheres is an important predictor of quality of life[18].

Fortunately, many of the barriers that we have identified are already the targets of

current treatments. For example, internal barriers, such as negative beliefs about relationships, have been targeted in Cognitive Behavioral Therapy for negative symptoms. Cognitive Behavioral Social Skills Training's[68,69] emphasis on communication and assertiveness skills and family therapy's focus on problem solving may assist with conflict-based barriers[70].

Although these findings provide an important step towards understanding what hinders and helps people with schizophrenia build social engagement, they should be considered in the context of limitations. First, our assessment of barriers and motivations was limited to participants' responses to the CAINS. Because specific barriers or motivations were not asked about explicitly, we may have undercounted, and we may not have captured all types of barriers (*e.g.*, social anxiety). Nevertheless, the CAINS includes more questions about social interactions than most clinical interviews, and thus the corpus of reported social engagement was richer than it might have been with a different interview.

Second, although we assessed the presence of barriers and motivations, we did not assess their relative contributions to impeding social engagement. For instance, although geographic distance (logistical barrier) and negative beliefs (internal barrier) may have been reported, it is possible that the negative beliefs were more impeding than distance. Third, the CAINS assessed the preceding and upcoming week, thus limiting the time period for reporting on social engagement. On the other hand, the strength of this approach is that it reduced difficulties and biases associated with retrospective reports. Fourth, all participants were taking antipsychotic medication so we cannot ascertain what, if any, impact medications may have had on participant responses. Finally, we did not assess related constructs, such as social network size, and thus future studies would benefit from investigating these alongside motivations and barriers to better understand the relationships between them.

CONCLUSION

In summary, we found that people with schizophrenia were less likely to interact with and initiate contact with friends compared to people without schizophrenia even as they did not differ in contact with family. Our findings suggest that certain types of social barriers get in the way of social engagement in schizophrenia, including barriers involving the self and conflicts with others. Importantly, social barriers and motivations were also related to real world functioning, suggesting that asking people to describe their social lives is linked to independent assessments of functioning. Together, our approach illustrates the benefits of simply asking people to describe their social lives and suggests that efforts to help mitigate social barriers might improve social engagement.

ARTICLE HIGHLIGHTS

Research background

Though limited social engagement is common in schizophrenia, the reasons for this remain unclear. People with schizophrenia report a desire to be with others, and yet spend more time alone.

Research motivation

Better understanding of the factors that contribute to limited social engagement can be an important first step toward helping people with schizophrenia to meet their social needs.

Research objectives

To identify and compare motivations and barriers for social engagement with friends and family among those with and without schizophrenia.

Research methods

Thirty-five people with schizophrenia or schizoaffective disorder and 27 nonclinical controls were recruited from the community to participate in this study. Participants completed measures of symptoms and functioning, as well as a negative symptoms interview, which asked participants to describe their engagement in and motivation

for social activities in the past and upcoming weeks. Using a novel coding system, we coded the frequency with which participants described six types of social motivations and barriers.

Research results

People with schizophrenia were less likely to interact with and initiate contact with friends, but not family, compared to nonclinical controls. The groups differed in reported barriers, such that people with schizophrenia reported more internal and conflict-based barriers than those without schizophrenia. People with and without schizophrenia reported similar numbers and types of motivations for social engagement. Barriers and motivations were associated with symptoms and functioning.

Research conclusions

This study suggests that barriers, such as conflicts with other people or negative beliefs about the self may interfere with social engagement in schizophrenia. People with schizophrenia report interest and motivation for social interactions, but social barriers may get in the way of them following through.

Research perspectives

Further exploration of social barriers in terms of types, frequency, and relative contribution to limiting social engagement is warranted.

ACKNOWLEDGEMENTS

The authors thank research assistants Apoorva Polisetty, Gregory Devine, Dania Smithstein, and Iliana Lopez Yanez, who helped with coding, and Gillian Chen, Renata Botello, Anna Deal, Janae Spinato, Alexandria Tu, Maryanna Winslow, and Alexandra Jensen, who helped with interview transcription. We also thank the people who chose to participate in this study.

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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 February 19; 11(2): 27-57



Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
February 19, 2021

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World Journal of Psychiatry

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World J Psychiatr 2021 February 19; 11(2): 27-34

DOI: 10.5498/wjp.v11.i2.27

ISSN 2220-3206 (online)

MINIREVIEWS

Sleep problems in children and adolescents following traumatic life events

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Author contributions: Kolaitis G conceived the original idea; Giannakopoulos G and Kolaitis G wrote the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

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Abstract

Rates of childhood trauma exposure are extremely high, with approximately 70% of children and adolescents experiencing at least one traumatic event. Among the most common non-specific consequences of stress and trauma are disruptions of sleep. Sleep problems, such as shorter sleep duration, difficulty falling asleep, frequent awakenings, nightmares, sleepless nights, and early-morning wakefulness appear to have a higher prevalence among children and adolescents following traumatic events. This review will illustrate the role of sleep problems in traumatized children and adolescents, and emphasize the need to consider a wide range of etiological mechanisms for these symptoms. However, the relationship of trauma exposure to sleep problems among children and adolescents needs further investigation in future research. Moreover, in view of the adverse consequences of long-term disrupted sleep on mental health outcomes following trauma, the need to effectively address sleep disturbances in traumatized children and adolescents is crucial.

Key Words: Child abuse; Natural disasters; Nightmares; Posttraumatic stress disorder; Sleep; Trauma and stressor related disorders

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Core Tip: Prevalence rates of child and adolescent posttraumatic stress disorder (PTSD) range from 0.5%-5%, while subthreshold PTSD and other trauma-related difficulties are relatively common among trauma-exposed children. Prevalence rates of sleep disturbances among trauma-exposed child samples vary considerably. Adverse effects of childhood trauma on sleep have been found immediately as well as years after

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: November 30, 2020
Peer-review started: November 30, 2020
First decision: December 21, 2020
Revised: December 21, 2020
Accepted: December 28, 2020
Article in press: December 28, 2020
Published online: February 19, 2021

P-Reviewer: Seeman MV
S-Editor: Fan JR
L-Editor: A
P-Editor: Li JH



trauma and can still be demonstrated in adulthood. Several hypotheses have been proposed to explain the mechanisms by which traumatic exposure may affect sleep. We discuss here the role of sleep problems in traumatized children and adolescents, and a broad range of etiological mechanisms for these symptoms.

Citation: Giannakopoulos G, Kolaitis G. Sleep problems in children and adolescents following traumatic life events. *World J Psychiatr* 2021; 11(2): 27-34
URL: https://www.wjgnet.com/2220-3206/full/v11/i2/27.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i2.27

INTRODUCTION

Rates of childhood trauma exposure are extremely high, with approximately 70% of children and adolescents experiencing at least one traumatic event[1,2]. Moreover, exposure to trauma during childhood leads to a number of negative physical and mental health outcomes[3-6]. Prevalence rates of posttraumatic stress disorder (PTSD) range from 0.5%-5%[1,7], while subclinical PTSD and trauma-related depression and behavioral problems are relatively frequent among trauma-exposed children[1,8-10].

Amidst the most prevalent general repercussions of stress and trauma are sleep disturbances. Sleep problems, such as shorter sleep duration, difficulty falling asleep, frequent awakenings, nightmares, sleepless nights, and early-morning wakefulness, appear to have a higher prevalence among children and adolescents following traumatic events[11-16].

Sleep occurs in every animal species and is essential for survival. It is comprised of dynamic patterns and gradual stages that take place during the night. Cohesion, timing, and ordering of these crucial stages are vital for adequate sleep[17]. Adequate sleep is linked to physical growth and psychological maturation, and is important for the optimal performance of vigilance systems[18-20]. Insufficient sleep has been associated with impaired daytime functioning, excessive tiredness, fatigue, pain, elevated blood pressure later in life, lesser regulation of affective reactions, elevated emotional dysregulation, aggression, anger, irritability, uneasiness, little frustration tolerance, high risk for developing substance use disorders, suicidal behaviors, problems sustaining attention, decreased performance on abstract reasoning tasks, and reduced academic performance in children and adolescents[21-32].

TRAUMA EXPOSURE AND SLEEP DISTURBANCES

In general population samples, approximately 16%-40% of children exhibit sleep disturbances[33-35]. Prevalence rates of sleep disturbances among trauma-exposed child samples vary considerably, from 3% to 77.1%[36-41]. Adverse effects of childhood trauma on sleep have been found immediately[42,43] as well as years after trauma[44], and can still be demonstrated in adulthood[45].

Nightmares are reported most commonly, although rates vary widely (20.3%–80.8%) depending on methodological discrepancies in sampling, measures, and informants about the child's symptoms. In fact, nightmares are a prototypic symptom of PTSD[46-52]. Nightmares have been included in the PTSD diagnostic formulation since its introduction in the Diagnostic Statistical Manual (DSM)-III[53] and have recently been expanded in DSM-5[54] to encompass sleep difficulties (as opposed to only nightmares). Recurrent distressing dreams and sleep disruptions (*e.g.*, difficulty falling or staying asleep, or restless sleep) are listed among the intrusion symptoms and the marked alterations in arousal and reactivity, respectively[54].

Sleep disturbances seem to be critically involved in PTSD development and maintenance[13,46]. Further, sleep difficulties seem to prevent recovery from traumatic events and to accelerate negative mental health outcomes[14,55,56]. Hence, trauma-related sleep problems in children and adolescents seem to be an important area of study. However, limited research has been conducted to date.

Characteristics of the traumatic event and associated risk factors may participate in understanding different types of sleep problems; still, these relationships are not well-known among children exposed to trauma.

Wamser-Nanney *et al*[57], in their study of 276 treatment-seeking children, showed that although sleep disturbances were common among trauma-exposed children, the type of traumatic event (*e.g.*, sexual abuse, physical abuse, domestic violence, emotional abuse, neglect, etc.) and the nature of trauma (*i.e.*, interpersonal *vs* non-interpersonal) or complex trauma were largely unrelated to sleep problems.

A study in 6132 adolescent survivors 3 years after a disastrous earthquake documented that older adolescents were at a significantly greater risk of sleep problems than younger children, and they had significantly higher risks of anxiety, depression, and PTSD. Other risk factors for sleep difficulties were characteristics of exposure to the earthquake, such as injury, injury of a parent, and witnessing death or feeling extremely scared in the earthquake[58]. Similarly, another cohort study[11] of 1573 adolescent survivors following a deadly earthquake found that the risk of sleep issues was significantly increased in older adolescents and in those who witnessed the tragic events directly. Depression, anxiety, poor social support, and negative life events were also associated with increased risk and persistence of sleep problems.

In a prospective study[17] of 78 females who had been sexually abused in childhood, it was found that sleep disturbances correlated significantly with both depression and PTSD 10 years after disclosure of the abuse. However, these traumatized youths showed significantly higher rates of sleep difficulties than the comparison group, in addition to depression and PTSD. Moreover, sleep difficulties were associated with revictimization rates independent of sexual abuse, depression, and PTSD.

A study on sleep quality across the developmental spectrum among avalanche survivors at 16 years after exposure showed that those who were children when the disaster occurred were more likely to report PTSD-related acting out dreams in adulthood than their non-exposed peers, while those who were adults at time of the disaster had elevated risk of trauma-related nightmares[59].

In a study of 33 children treated for injuries after road traffic accidents, it was shown that children experiencing posttraumatic stress had a prolonged subjective sleep latency[60]. Moreover, the severity of difficulties in sleep onset and maintenance was associated with female gender and the severity of child's and mothers' PTSD.

ETIOLOGICAL MECHANISMS

Caldwell and Redeker[18] have claimed that more extensive research is needed in order to improve our understanding of the elevated sleep problems among children and adolescents following trauma. Several hypotheses have been proposed to explain the mechanisms by which traumatic exposure may affect sleep (Table 1).

According to a biological perspective, traumatic stress may be related to increased levels of physiological arousal, that hinders conditions crucial for sleep onset. In fact, sleep onset problems may be more prominent compared to sleep maintenance problems among traumatized children[44,60]. It has been claimed that increased activity of the amygdala and decreased activity of the medial prefrontal cortex sustain or enhance activity in arousal-promoting brain centers and diminish activity in sleep-promoting centers[61]. The emerging pattern of enduring arousal could directly conduce to insomnia problems.

Sleep is naturally restricted to times and places that feel safe. If arousal is increased by cause of imminent threat, sleep will possibly deteriorate[25]. Safety is a notably pertinent concern for children and adolescents exposed to trauma. Moore[62], for example, concluded that interpersonal trauma hinders development of a safe attachment style, leading to the feeling that one needs to be continuously alert and on guard instead of sleeping.

Levin *et al*[63] proposed a conceptual framework for understanding disturbed dreaming following traumatic stress that accommodate data on emotional memory structures and the brain correlates of emotion. A fundamental assumption in this model is that alterations in nightmare rates, severity, and comorbidity reflect the influence of both affect load, a consequence of daily alterations in emotional pressure, and affect distress, an inclination to distressing, highly reactive emotional experiences.

The threat simulation theory of dreaming[64] states that threat simulation in the course of dreaming reenacts the cognitive mechanisms needed for adequate threat perception and threat avoidance. An assumption drawn from this theory is that real threatening events experienced throughout wakefulness may result in a heightened activation of the threat simulation system, and thus, to an elevated recurrence and severity of threatening experiences in dreams. Therefore, children living in conditions in which their physical and psychological well-being is continually jeopardized may

Table 1 Hypothetical mechanisms by which traumatic exposure may affect sleep

Hypothesis	Mechanism
Biological perspective	Physiological arousal (increased activity of the amygdala, and decreased activity of the medial prefrontal cortex) hinders sleep onset
Safety and attachment	Feeling that one needs to be continuously alert and on guard instead of sleeping
Emotional memory and affect	Alterations in nightmare rates, severity, and comorbidity reflect the influence of both affect load and distress
Threat simulation theory	Threat simulation in the course of dreaming reenacts the cognitive mechanisms needed for adequate threat perception and threat avoidance
Emotional regulation model	Individuals exposed to trauma continue to be hyper-alert to defend themselves against real or imagined hazards, such as through distressing dreaming that replays the traumatic experience during sleep
Hyperarousal-based theory	Under a hyper-arousal state, trauma survivors show an increased level of awareness and a sensitized response to the external world
Anxiety buffer disruption assumption	Fear can increase the likelihood of gathering traumatic cues in the cognitive world, resulting in intrusive thoughts
Depressive-like pathophysiology	Elevated plasma cortisol levels near sleep onset, increased sleep latency, and significant dysregulation in REM sleep patterns
Cognitive hyperactivation	Excessive worry, rumination, and negative attributions contribute to the hyperarousal interfering with sleep

REM: Rapid eyes movement.

have an extremely triggered dream production and threat simulation system. Valli *et al*[65] examined this assumption by analyzing the content of dream reports from markedly traumatized and less traumatized Kurdish children and non-traumatized Finnish children. The researchers found that the markedly traumatized children expressed a significantly higher number of dreams and their dreams involved a greater number of threatening dream experiences. Also, the nature of dream threats of traumatized children was more serious than the threats of less traumatized or non-traumatized children.

An analogous model, the emotional regulation model of trauma[66] proposes that there is a fear network that connects fear-related information in a traumatized individual's memory[67]. This information can be triggered by real or imagined trauma-related cues, and a fear response will then be evoked. Hence, individuals exposed to trauma may continue to be hyper-alert to defend themselves against real or imagined hazards, such as through distressing dreaming that replays the traumatic experience during sleep[68]. This is also supported by the finding that traumatized individuals show elevated arousal activity during sleep, which in turn leads to a lighter or more fragmented sleep[12]. Thus, fear could be a risk factor for the onset of sleep difficulties following a traumatic event.

The hyperarousal-based theory of sleep problems[69] proposes that PTSD leads to a hyper-arousal state, under which traumatized individuals will experience an increased level of awareness and a sensitized response to the external world. Hyper-arousal breaks the necessary prerequisite for optimal sleep quality and makes sleep problems more noticeable[70]. Furthermore, PTSD can also cause trauma survivors to re-experience the trauma-related cues in their cognitive world, therefore eliciting the physiological arousal and undesirable emotions that will in turn disturb their sleep[71].

Moreover, the anxiety buffer disruption assumption[72] suggests a close association between fear and PTSD. This assumption highlights that fear can increase the likelihood of gathering traumatic cues in the cognitive world, resulting in intrusive thoughts related to hyper-arousal states[67]. It is also suggested that the fear can exacerbate the severity of PTSD through hampering the constructive examination of traumatic experiences and the consolidation of traumatic memories[73,74].

In support of the emotional regulation model of trauma and the hyperarousal-based theory, Zhou *et al*[75] showed that fear and PTSD among adolescents 1 year after an earthquake mediated the relationship between trauma exposure at 1 year following the earthquake, and sleep difficulties at both 1 year and 1.5 years following the earthquake, respectively. Moreover, Zhou *et al*[76] found that intrusive, avoidance and hyperarousal symptom clusters of PTSD could be significant predictors for the emergence and persistence of sleep difficulties from 1 year to 1.5 years after the earthquake. The intrusive symptoms of PTSD may increase the frequency of cognitive

activities[77], and hyperarousal symptoms can elevate the physiological or psychological hyperarousal state[12,78]; adolescents with symptoms of avoidance may seek to avoid being dominated by traumatic cues during dreaming by avoiding falling asleep[67]. However, in the study by Zhou *et al*[76], from 1.5 years to 2 years following the earthquake, only the avoidance symptom clusters of PTSD were risk factors for sleep difficulties and the relationship between PTSD and sleep problems weakened with time change.

Last, it has been suggested that mechanisms for sleep disturbances, such as elevated plasma cortisol levels near sleep onset, increased sleep latency, and significant dysregulation in rapid eyes movement, sleep patterns, parallel aspects of underlying pathophysiology of severe adolescent depression[79]. Moreover, the depressive cognitive hyperactivation (*i.e.*, excessive worry, rumination, and negative attributions) may contribute to the hyperarousal interfering with sleep.

CONCLUSION

The present review illustrates the role of sleep difficulties in children and adolescents exposed to trauma and emphasizes the need to examine a wide range of etiological mechanisms for these symptoms. However, the relationship of trauma exposure to sleep problems among children and adolescents needs further investigation in future research. For example, work is needed to understand the mechanisms by which sleep difficulties emerge and persist in the context of childhood trauma, and if sleep problems exacerbate other trauma-related symptoms. Additionally, the long-term course of sleep problems in children exposed to trauma have not been thoroughly reported.

Moreover, in view of the negative consequences of long-term disrupted sleep on mental health outcomes following trauma, the need to effectively address sleep disturbances in traumatized children and adolescents is crucial. Thus, clinicians should be aware of sleep problems in childhood trauma victims. Trauma-focused interventions for children and adolescents may be beneficial not only for relieving child and adolescent traumatic stress but also for ameliorating adolescents' sleep problems, and could be complemented by tailored psychotherapeutic and pharmacological interventions targeting sleep disturbances.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 February 19; 11(2): 35-49

DOI: 10.5498/wjp.v11.i2.35

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Basic Study

Selective ablation of type 3 adenylyl cyclase in somatostatin-positive interneurons produces anxiety- and depression-like behaviors in mice

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Author contributions: Yang XY and Cao H designed and coordinated the study; Yang XY and Ma ZL performed the experiments, acquired, and analyzed data; Storm DR provided the Floxed AC3 mice; Cao H and Zhang YQ interpreted the data; Yang XY, Storm DR and Cao H wrote the manuscript; All authors approved the final version of the article.

Supported by National Natural Science Foundation of China, No. 81771208 and No. 81971043

Institutional animal care and use committee statement: The study was reviewed and approved by the Experimental Animal Ethics Committee of Shanghai Medical College and the Institutional Animal Care & Use Committee (IACUC) of Fudan University (permit No. 20170223-091). All experimental procedures were designed to minimize pain or discomfort to the animals and followed the ethical guidelines of

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Abstract

BACKGROUND

Major depressive disorder (MDD) is a highly disabling psychiatric syndrome associated with deficits of specific subpopulations of cortical GABAergic interneurons; however, the underlying molecular mechanism remains unknown. Type 3 adenylyl cyclase (ADCY3, AC3), which is important for neuronal excitability, has been implicated in MDD in a genome-wide association study in humans. Moreover, a study reported that ablation of AC3 in mice caused similar symptoms as MDD patients.

AIM

To determine if disruption of the AC3 gene in different subtypes of GABAergic interneurons of mice causes depression-like behaviors.

METHODS

Using immunohistochemistry, we investigated the expression of AC3 in two major subtypes GABAergic interneurons: Somatostatin-positive (SST^+) and parvalbumin-positive (PV^+) neurons. Genetic manipulations were used to selectively disrupt AC3 expression in SST^+ or PV^+ interneurons. A series of behavior tests including rotarod test, open field test (OFT), elevated plus maze test (EPM), forced swimming test (FST), and tail suspension test (TST) were used

the International Association for the Study of Pain regarding the use of laboratory animal.

Conflict-of-interest statement: All authors have no any conflicts of interest.

Data sharing statement: No additional data are available.

ARRIVE guidelines statement: The authors have read the ARRIVE Guidelines, and the manuscript was prepared and revised according to the ARRIVE Guidelines.

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Manuscript source: Unsolicited manuscript

Specialty type: Psychiatry

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: October 13, 2020
Peer-review started: October 13, 2020
First decision: December 4, 2020
Revised: December 9, 2020
Accepted: December 24, 2020
Article in press: December 24, 2020
Published online: February 19, 2021

P-Reviewer: Contreras CM
S-Editor: Huang P
L-Editor: Filipodia

to evaluate the motor ability, anxiety- and depression- like behaviors, respectively.

RESULTS

Our results indicate that approximately 90.41% of SST$^+$ and 91.22% of PV$^+$ interneurons express AC3. After ablation of AC3 in SST$^+$ interneurons, the mice spent comparable time in the center area in OFT, but significantly less time in the open arms and low frequency of entries to the open arms in EPM. Furthermore, these mice showed prolonged immobility in FST and more freezing in TST. However, there were no significant changes in these behaviors after specific disruption of AC3 in PV$^+$ interneurons.

CONCLUSION

This study indicates that ablation of AC3 in SST$^+$ interneurons of mice increases anxiety- and depression-like behaviors in mice, supporting the general hypothesis that decreased AC3 activity may play a role in human depression.

Key Words: Type 3 adenylyl cyclase; Somatostatin; Parvalbumin; Anxiety; Depression; Mice

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Core Tip: Dysfunction of cortical GABAergic interneurons are thought to contribute to the pathophysiology of stress-related psychiatric disorders. Little is known about the regulation of GABAergic interneurons in depression. Type 3 adenylyl cyclase (AC3) is important for the neuronal excitability and was reported as a top-ranked gene in major depressive disorder (MDD). Here, we found that majority of somatostatin-positive (SST$^+$) and parvalbumin-positive (PV$^+$) GABAergic interneurons express AC3. Selective disruption of AC3 in SST$^+$ but not PV$^+$ interneurons caused anxiety- and depression-like behaviors. Our data suggest that AC3 in specific subtype interneurons played a key role in the etiology of depression, providing new insights for therapeutic interventions for the treatment of MDD.

Citation: Yang XY, Ma ZL, Storm DR, Cao H, Zhang YQ. Selective ablation of type 3 adenylyl cyclase in somatostatin-positive interneurons produces anxiety- and depression-like behaviors in mice. *World J Psychiatr* 2021; 11(2): 35-49
URL: https://www.wjgnet.com/2220-3206/full/v11/i2/35.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i2.35

INTRODUCTION

Major depressive disorder (MDD) is a severe psychiatric disorder that affects up to one in six individuals worldwide[1]. Despite long-lasting efforts to explore the etiology and pathophysiology of depression, the underlying neurobiological mechanisms are not well defined. Current antidepressant pharmacological treatments are mainly focused on monoaminergic neurotransmission, which is based on the traditional catecholamine and serotonin hypotheses of mental disorders[2,3]. However, only approximately 33% of patients experience remission after pharmacological treatments, and up to one-third of these patients have a poor response to regular antidepressant treatments[4,5]. Therefore, it is important to identify new drug target sites for treatment of depression.

Recent evidence suggests that the functional interaction between the glutamatergic excitatory and GABAergic inhibitory connectivity is altered during depression and chronic stress exposure[6-8] suggesting that impairment of γ-aminobutyric acid (GABA) neurotransmission may contribute to the neurobiology of MDD[9,10]. The cortical GABAergic interneurons are divided into different subtypes according to their morphology, electrophysiological properties, and expression of calcium-binding proteins and neuropeptides[11]. Most research concerning GABAergic interneurons in depression and anxiety has focused on two major subtypes expressing somatostatin (SST) or parvalbumin (PV), which make up approximately 70% of GABAergic

P-Editor: Li JH

inhibitory neurons[12,13]. Studies focusing on SST in MDD suggest a reduction of SST in several corticolimbic brain regions in postmortem MDD patients, including the dorsolateral prefrontal cortex, subgeual anterior cingulate cortex (sgACC), and amygdala[14-16]. Mice lacking SST (SST global knockout mice) display similar behavioral and molecular features as human depression. This includes increased circulating corticosterone, elevated anxiety/depressive-like behaviors, and reduced gene expression of brain-derived neurotrophic factor (BDNF), cortistatin, and glutamate decarboxylase 67 (GAD67)[17]. However, there is less evidence for consistent alterations of PV^+ interneurons in MDD. Most studies have reported that there are no significant changes in PV expression in either MDD subjects[18-21] or rodent models[21-24]. Several studies have indicated decreased PV expression in tissues of post-mortem MDD patients[21] or in rodent models[20,25]. By contrast, increased PV expression has been reported when female mice are exposed to unpredictable chronic stress for 2 wk[26]. Since SST^+ and PV^+ interneurons differentially target specific cellular domains (distal dendritic *vs* perisomatic regions) of pyramidal neurons and other interneurons, it is reasonable to believe that they might play different roles in the pathology of MDD.

Type 3 adenylyl cyclase (AC3, ADCY3), is widely expressed in primary cilia in neurons of the central nervous system[27]. AC3 is stimulated by Gs-coupled receptors and inhibited by Gi-coupled receptors and Ca^{2+}/calmodulin-dependent protein kinase II[28]. In 2012, a genome-wide association study in humans implicated the *ADCY3* gene in MDD[29]. Moreover, a study published by Chen *et al*[30] showed that $AC3^{-/-}$ mice have similar symptoms as MDD patients. This includes increased rapid eye movement sleep time, anosphrasia, and anxiety and -depression-like behaviors.

However, there is little information on how decreases in AC3 activity contribute to the pathophysiological process of MDD. In this study, we took advantage of several transgenic mice lines. We bred $AC3^{flox/flox}$ mice with subtype-specific GABAergic interneuron Cre lines in which the Cre recombinase (Cre) is expressed under the control of SST or PV promoters to explore the roles of AC3 in SST^+ and PV^+ interneurons in the development of anxiety and depression mood disorders.

MATERIALS AND METHODS

Animals

Male C57BL/6J mice were obtained from the Shanghai Experimental Animal Center of the Chinese Academy of sciences. $AC3^{flox/flox}$ mice were generated as previously reported[30]. SST-Cre mice (JAX013044), PV-Cre mice (JAX008069), and Ai14 mice (JAX007914) were purchased from Jackson Laboratory (Bar Harbor, ME, United States). All mice were backcrossed into the C57BL/6J genetic background for at least six generations. Mice were genotyped using their tail tissue after cracking by lysis reagent (Direct PCR Lysis Reagent [mouse tail], QIAGEN, Hilden, Germany) and proteinase K (Proteinase K, QIAGEN). Seventy-eight male mice used in behavioral analysis were age 8-12 wk old with comparable body weight. Eleven male adult mice were used for immunohistochemistry. All mice were group-housed (3-6 per cage) and maintained on the a 12/12 h light/dark cycle, 50% humidity, at 23.1 °C with access to food and water *ad libitum*. All experimental procedures were designed to minimize pain or discomfort to the animals, approved by the Experimental Animal Ethics Committee of Shanghai Medical College and the Institutional Animal Care & Use Committee (IACUC) of Fudan University (Permit No. SYXK2009-0082; Shanghai, China) and followed the ethical guidelines of the International Association for the Study of Pain regarding the use of laboratory animals.

Behavioral studies

Mice were handled at least 3 d by the experimenters before the behavioral tests, and habituated to the test room for 30 min before behavioral test. All behavioral tests were performed by investigators blind to genotypes.

Accelerating rotarod test

The rotarod test was performed as previously described[31]. Briefly, the mice were placed on an accelerating rotarod (IITC Life Science, Woodland Hills, CA, United States) (4-40 rpm acceleration in 5 min) for 4 consecutive days. Training consisted of 4 trials per day at 5 min intervals. The trial ended when the mouse fell off the roller. We calculated the average latency to fall from the last two trials performed on the last day.

Open field test

The apparatus consisted of a square box (40 cm × 40 cm × 30 cm, length × width × height) with blue floor and without a celling. Both the box and floor were made of Perspex plates. During testing, the floor was separated into 16 small squares of equal area. The four squares in the center were designated the central area, and the others are called the limbic area. The light level was maintained at approximately 25 lux in the open field area. The test began when the mice were put in the center of the square. After free movement for 5 min, the mice were returned to their home cages. Video tracking software (Ethovision XT v11.5; Noldus Information Technology Inc., Leesburg, VA, United States) was used to record the distance traveled and time spent in each zone.

Elevated plus maze test

The elevated plus maze consisted of a central platform (6 cm, 6 cm), two open arms (30 cm, 6 cm) and two closed arms (30 cm, 6 cm) with protective walls 15 cm high. The apparatus was elevated 50 cm above the floor and was placed in a room with an illumination of 30 lux. Mice were put on the central platform facing an open arm, and allowed to freely explore the maze for 5 min. The traces were recorded by the video tracking system (Ethovision XT v11.5; Noldus BV). The time spent exploring time in the open arm and the frequency of entries to the open arm were calculated by Video Tracking software (Ethovision XT v11.5; Noldus BV).

Forced swimming test

Mice swam individually in a cylindrical glass container (diameter: 18 cm, height: 50 cm, depth: 12 cm) filled with water (24.1 °C). The test comprised two sessions: A training session (10 min) on the first day and a test session (5 min) on the next day, which were recorded by a video camera. Immobility in mice was defined as no active movements except for single limb paddling to keep the head and nose above the water.

Tail suspension test

The apparatus for the tail suspension test (TST) was a white plexi-glass box with a hook on the ceiling of the box. The mice were suspended 15 cm above the floor on the hook with a tape at 2 cm proximal to the tail tip. The test session lasted 6 min and was recorded with a video camera. The freezing time was scored for the last 4 min of the session.

Immunohistochemistry

Mice were deeply anesthetized with urethane (1.5 g/kg) and perfused transcardially with normal saline followed by 40 g/L paraformaldehyde in phosphate-buffered saline (PBS). The brains were collected, post-fixed in the same fixative for additional 4 h at 4 °C, and dehydrated in graded sucrose solutions (10 g/L, 20 g/L, 30 g/L). Continuous coronal sections of brains (35 μm) were prepared on a cryostat (Leica, Germany) and stored at -20 °C. Sections were washed with 0.01 mol/L PBS and blocked in 10% donkey serum in 0.01 mol/L PBS, pH 7.4, with 0.3% Triton X-100 for 2 h at room temperature (RT). For triple immunostaining of SST/AC3/NeuN, SST-Cre:Ai$^{f/f}$reporter mice were used. Sections were incubated with a mixture of rabbit anti-AC3 (1:1000, SC-588; Santa Cruz, Dallas, TX, United States) and mouse anti-NeuN (1:1000, MAB377; Millipore, Burlington, MA, United States), followed by the corresponding secondary antibodies (1:200, Alexa Fluor 647 donkey anti-rabbit, 711-605-152, Jackson Laboratory; 1:200, Alexa Fluor 488 donkey anti-mouse, A-21202, Invitrogen, Carlsbad, CA, United States) for 2 h at 4 °C. For triple immunostaining of PV/AC3/DAPI, the sections were incubated with a mixture of rabbit anti-AC3 and mouse anti-PV (1:500, P3088; Sigma, St. Louis, MO, United States) overnight at 4 °C, followed by their corresponding secondary antibodies (1:200, Alexa Fluor 546 donkey anti-rabbit, A-10040, Invitrogen; 1:200, Alexa Fluor 488 donkey anti-mouse, A-21202, Invitrogen) for 2 h at 4 °C. The nuclei were counterstained with DAPI (1:20000, 62248; Thermo Fisher Scientific, Waltham, MA, United States) for 3 min at RT. All sections were coverslipped with a mixture of 50% glycerin in PBS. Images were captured with a confocal laser-scanning microscope (FV1000; Olympus, Tokyo, Japan). The interval between two adjacent focal planes was 2 μm (*z*-stack). Image analysis was performed by Photoshop or FV10-ASW 1.7 Viewer software (Olympus).

Fluorescent in situ hybridization using RNAscope and double staining with immunohistochemistry

Brain sections (14 μm) were cut using a cryostat and mounted onto Colorfrost Plus slides (Thermo Fisher Scientific). In situ hybridization (ISH) was performed using the RNAscope system (Advanced Cell Diagnostics, Newark, CA, United States) according to the manufacturer's protocol. Sections were pretreated with hydrogen peroxide for 10 min at RT, followed by target-retrieval solution and Protease III using RNAscope 2.5 Universal Pretreatment Reagents (#322381; Advanced Cell Diagnostics). Then the commercial probe for AC3 (#478071-C1) was used. After hybridization, the RNAscope Multiplex Fluorescent Detection Kit v2 (#323110) was used to amplify signal. After ISH, sections were labeled with anti-SST antibody (goat, 1:500, sc-7819; Santa Cruz), followed by its corresponding secondary antibody (Alexa Fluor 488 donkey anti-goat, 1:200, A-11055; Invitrogen). Images were captured with a confocal laser-scanning microscope (Model FV1000; Olympus).

Statistical analysis

All data are presented as the mean ± standard error of the mean and were analyzed using Prism 7.0 (GraphPad Software, San Diego, CA, United States). Comparisons between two groups were performed using the two-sided Student's *t*-test. One way analysis of variance (ANOVA) followed by post hoc Tukey's multiple comparisons test was used for data comparison between three groups. $P < 0.05$ was considered statistically significant.

RESULTS

Expression of AC3 in SST$^+$ and PV$^+$ interneurons in mice

As a starting point, we examined the expression of AC3 in two major subtypes of cortical GABAergic interneurons. As shown in Figure 1, AC3 immunostaining was extensively distributed in the brain area examined (Figure 1A and D). Consistent with previous reports[27], the high magnification of imaging showed that AC3 was exclusively expressed in primary cilia with a rod-like shape (Figure 1B and E). To observe the expression of AC3 in SST$^+$ interneurons, we bred SST-Ai14$^{f/f}$ transgenic mice in which SST$^+$ interneurons were labeled with the tdTomato fluorescent protein carried by the *Ai14* gene. Statistical analysis showed that approximately 90.41% of SST$^+$ interneurons expressed AC3 (Figure 1C). We also examined the expression of AC3 in PV$^+$ interneurons using double immunostaining. Similar to SST$^+$, about 91.22% of PV$^+$ interneurons expressed AC3 (Figure 1F). Our results indicated that the majority of SST$^+$ and PV$^+$ GABAergic interneurons express AC3.

Deletion of AC3 from SST$^+$ neurons results in anxiety- and depression-like behaviors

To explore the functional role of AC3 in specific cell type interneurons, SST-Cre mice, PV-Cre mice, and AC3$^{flox/flox}$ mice in which exon 3 of the *ADCY3* gene was flanked by two loxP sites were used. We assessed a series of general behaviors of AC3$^{flox/flox}$ mice that served as controls. As shown in Figure 2, the behaviors of AC3$^{flox/flox}$ mice analyzed in the open field test (OFT) (Figure 2A), elevated plus maze (Figure 2B), forced swimming test (FST) (Figure 2C), TST (Figure 2D) and rotarod test (Figure 2E) were largely indistinguishable from wild-type mice, indicating that the floxed AC3 mice showed normal emotion-related behaviors and motor ability.

To characterize the functional role of AC3 in SST$^+$ neurons, we generated SST-Cre:AC3$^{f/f}$ mice by breeding SST-Cre mice and AC3$^{flox/flox}$ mice to selective delete AC3 from SST$^+$ interneurons (Figure 3A). As expected, the immunoreactivity of *ACDY3* transcript examined by RNAscope IST disappeared in SST$^+$ interneurons in SST-Cre:AC3$^{f/f}$ mice but not in AC3$^{flox/flox}$ mice (Figure 3B). Then we subjected SST-Cre:AC3$^{f/f}$ mice to test for anxiety- and depression-like behaviors. In the OFT, although the SST-Cre:AC3$^{f/f}$ mice moved less distance in the apparatus compared with the other two groups (one-way ANOVA, $F_{(2, 32)} = 3.871$, $P = 0.0312$; Figure 3C), the SST-Cre:AC3$^{f/f}$ mice did not show an obvious difference in the ratio of moving distance in central area and the center area duration (one-way ANOVA, $F_{(2, 32)} = 0.2423$, $P = 0.7863$, Figure 3D; one-way ANOVA, $F_{(2, 32)} = 0.0471$, $P = 0.9541$, Figure 3E). In the elevated plus maze test, the total entry frequency of both arms in SST-Cre:AC3$^{f/f}$ mice was significantly lower than that in the AC3$^{flox/flox}$ mice and SST-Cre mice (one-way ANOVA, $F_{(2, 32)} = 14.62$, $P < 0.0001$; Figure 3F). Further analysis revealed that SST-Cre:AC3$^{f/f}$ mice spent less time in the open arms (one-way ANOVA, $F_{(2, 32)} = 6.052$, $P = 0.0062$; Figure 3G) and a decreased

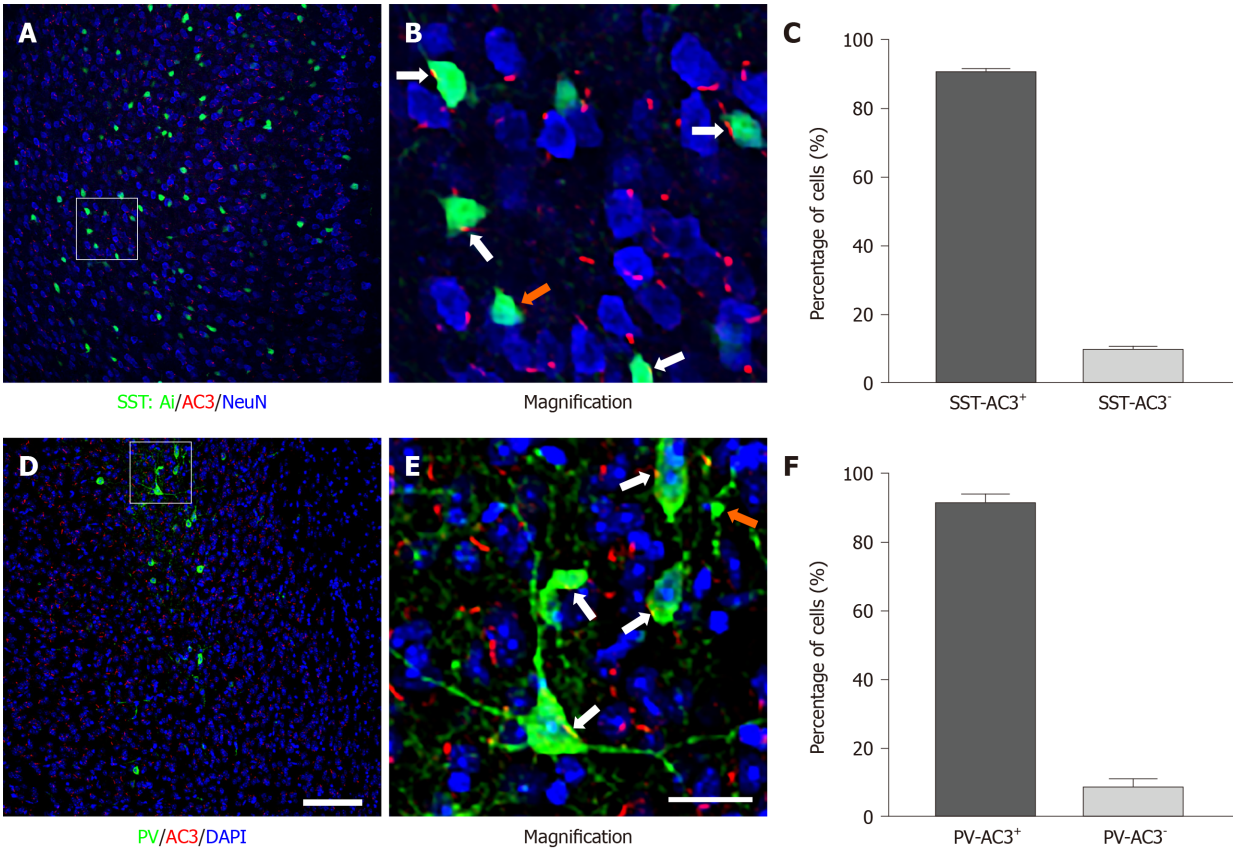


Figure 1 Expression of type 3 adenylyl cyclase in cortical somatostatin-positive and parvalbumin-positive GABAergic interneurons. A and B: Representative images showing type 3 adenylyl cyclase (AC3) expression in somatostatin-positive (SST$^+$) interneurons at low (A) and high (B) magnifications in the prefrontal cortex brain slice. Solid arrows in B indicate SST$^+$ interneurons, which are also AC3-positve (SST-AC3$^+$ cells). Empty arrow in B indicates SST$^+$ interneurons, which are AC3-negative (SST-AC3$^-$ cells); C: Proportion of AC3 expressed in cortical SST$^+$ neurons, n = 6; D and E: Representative images showing AC3 expression in parvalbumin-positive (PV$^+$) interneurons at low (D) and high (E) magnifications in the prefrontal cortex brain slice. Solid arrows indicate PV$^+$ interneurons, which are also AC3-positve (PV-AC3$^+$ cells). Empty arrow in E indicates PV$^+$ interneurons, which are AC3-negative (PV-AC3$^-$ cells); F: Proportion of AC3 expressing in cortical PV$^+$ neurons, n = 5. Scale bars represent 100 μm in D and 20 μm in E, respectively.

percentage of open arms entries (one-way ANOVA, $F_{(2, 32)}$ = 6.768, P = 0.0035; Figure 3H) relative to AC3$^{flox/flox}$ mice and SST-Cre mice.

We also used the FST and TST to evaluate the depression level of the mice, since anxiety and depression are common comorbid psychiatric disorders among patients. SST-Cre:AC3$^{f/f}$ mice showed increased immobility time in the FST (one-way ANOVA, $F_{(2, 32)}$ = 11.32, P = 0.0002; Figure 4A), and prolonged freezing time in TST (one-way ANOVA, $F_{(2, 32)}$ = 8.509, P = 0.0011; Figure 4B) compared with AC3$^{flox/flox}$ mice and SST-Cre mice. These data suggest that the SST-Cre:AC3$^{f/f}$ mice exhibit depression-like behaviors in two different test paradigms. There was no significant difference between the AC3$^{flox/flox}$ group and SST-Cre mice in these behavioral tests.

Deletion of AC3 from PV$^+$ neurons did not influence anxiety- and depression-like behaviors

PV$^+$ interneurons are another major group of GABAergic interneurons which are thought to play a vital role in mood disorders. Whether ablation of AC3 in PV$^+$ interneurons influences anxiety- or depression-like behaviors was unknown. Here, AC3$^{flox/flox}$ mice were crossed with the PV-Cre mice for specific disruption of AC3 expression in the PV$^+$ interneurons (Figure 5A). Ablation of AC3 expression in PV$^+$ GABAergic interneurons in PV-Cre:AC3$^{f/f}$ mice, but not in control AC3$^{flox/flox}$ mice, was confirmed by double immunostaining (Figure 5B). Then we examined PV-Cre:AC3$^{f/f}$ mice for anxiety- and depression-like behaviors. The PV-Cre:AC3$^{f/f}$ mice moved a similar total distance and percentage of central distance (one-way ANOVA, $F_{(2, 25)}$ = 0.2446, P = 0.7849, Figure 5C; one-way ANOVA, $F_{(2, 25)}$ = 0.08463, P = 0.9191, Figure 5D) and spent a similar period of time in the center arena of the open field (one-way ANOVA, $F_{(2, 25)}$ = 0.246, P = 0.7838; Figure 5E) either to control AC3$^{flox/flox}$ or PV-Cre mice. These mice also spent comparable time in the open arms (one-way ANOVA, $F_{(2, 25)}$ = 0.1231, P = 0.8847; Figure 5G) and the entries to both arms and the frequency of

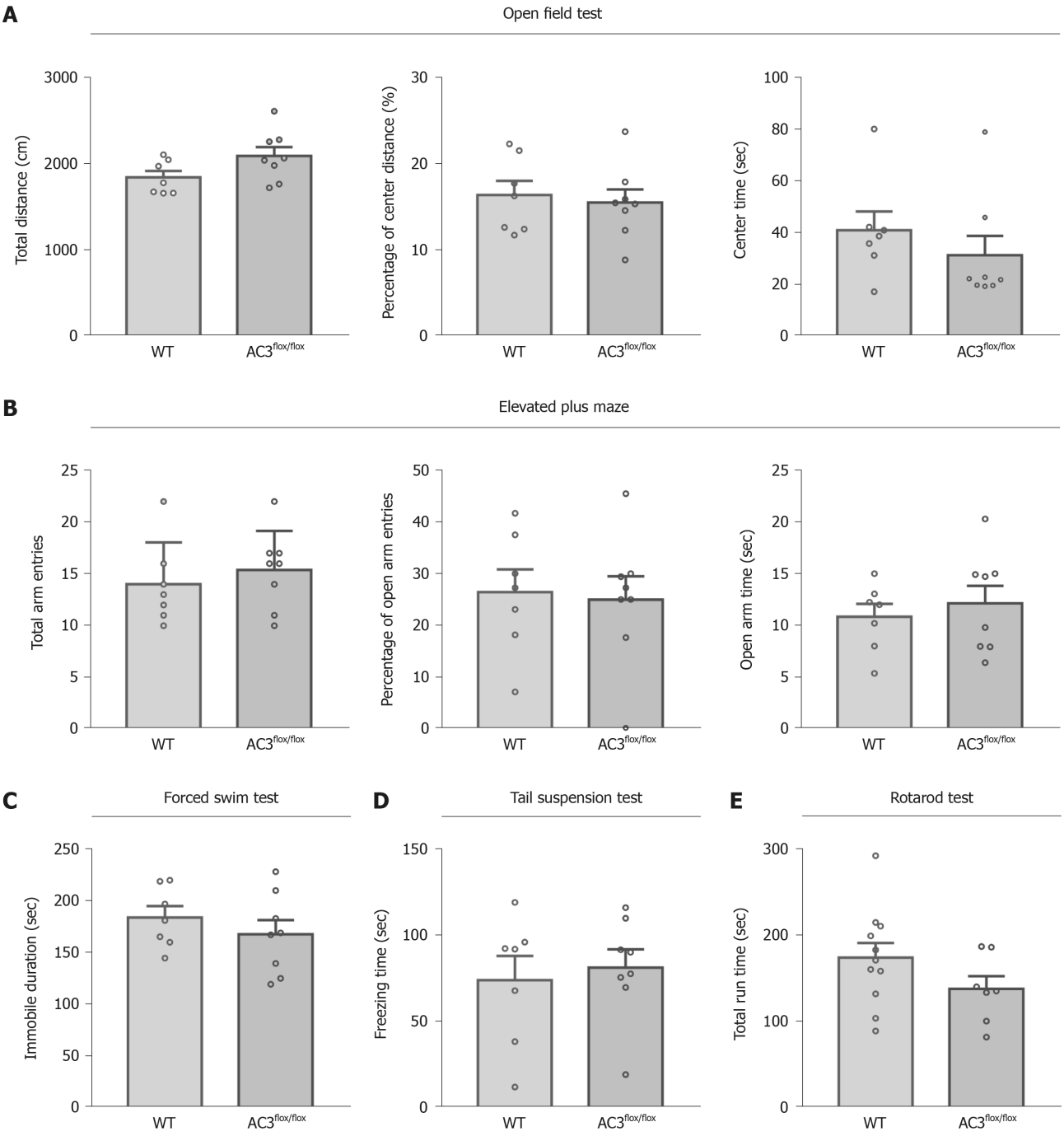
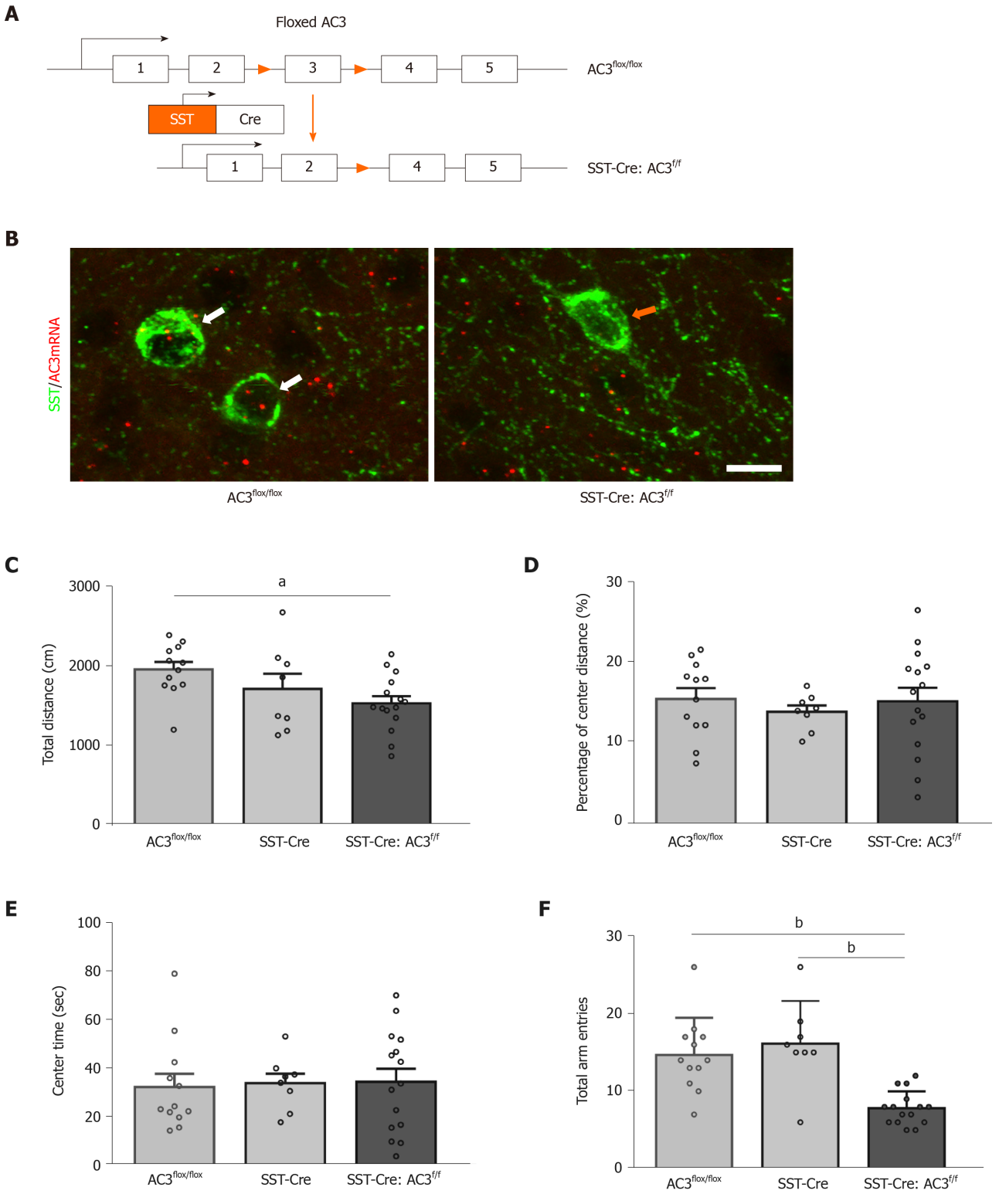


Figure 2 Type 3 adenylyl cyclase$^{flox/flox}$ mice exhibit normal emotion-related behaviors and motor ability compared with wild-type C57 mice.
A and B: Anxiety-related behavioral tests were illustrated by the open field test (A) and elevated plus maze (B); C and D: Depression-like behavioral tests were examined by the forced swimming test (C) and tail suspension test (D); E: Motor ability was examined by the rotarod test. Bars represent the mean ± standard error of the mean. Data were analyzed using the Student's *t*-test. n = 7 for the wild-type (WT) group, n = 8 for the type 3 adenylyl cyclase (AC3)$^{flox/flox}$ group.

entries to the open arms is similar compared with AC3$^{flox/flox}$ mice and PV-Cre mice (one-way ANOVA, $F_{(2, 25)}$ = 0.082, P = 0.9219, Figure 5F; one-way ANOVA, $F_{(2, 25)}$ = 0.7036, P = 0.5044, Figure 5H). Also, there was no significant differences in the immobility in the FST (one-way ANOVA, $F_{(2, 25)}$ = 0.3572, P = 0.7032, Figure 6A) or the freezing time in the tail-suspension test when selective deletion of AC3 in PV^{+} interneurons (one-way ANOVA, $F_{(2, 25)}$ = 0.136, P = 0.8735, Figure 6B). Taken together, PV-Cre:AC3$^{f/f}$ mice did not exhibit a pro-anxiety or pro-depression phenotype.


A
Floxed AC3
1
2
3
4
5
AC3flox/flox
SST
Cre
1
2
4
5
SST-Cre: AC3f/f
B
SST/AC3mRNA
AC3flox/flox
SST-Cre: AC3f/f
C
Total distance (cm)
3000
2000
1000
0
a
AC3flox/flox
SST-Cre
SST-Cre: AC3f/f
D
Percentage of center distance (%)
30
20
10
0
AC3flox/flox
SST-Cre
SST-Cre: AC3f/f
E
Center time (sec)
100
80
60
40
20
0
AC3flox/flox
SST-Cre
SST-Cre: AC3f/f
F
Total arm entries
30
20
10
0
b
b
AC3flox/flox
SST-Cre
SST-Cre: AC3f/f

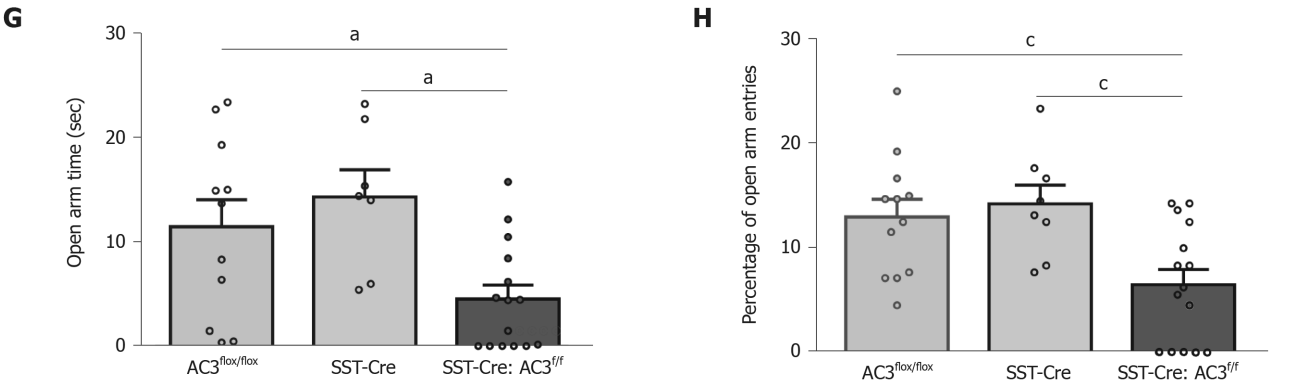


Figure 3 Somatostatin-positive-Cre recombinase:type 3 adenylyl cyclase$^{f/f}$ **mice showed anxiety-like behavior.** A: Strategy for generation of somatostatin-positive-Cre recombinase: type 3 adenylyl cyclase$^{f/f}$ (SST-Cre:AC3$^{f/f}$) mice in which type 3 adenylyl cyclase (AC3, ADCY3) was selectively ablated in SST$^+$ interneurons; B: Fluorescence in situ hybridization showing the representative micrographs of ADCY3 mRNA expression (red) in SST$^+$ interneurons (green) from AC3$^{flox/flox}$ control mice (left) and SST-Cre:AC3$^{f/f}$ mice (right). Solid arrows indicated that SST$^+$ interneurons are co-expressed ADCY3 mRNA in AC3$^{flox/flox}$ control mice. Empty arrow indicated that ADCY3 mRNA fluorescence is missing in SST$^+$ interneurons in SST-Cre:AC3$^{f/f}$ mice. Scale bar: 10 μm; C-E: Showing SST-Cre:AC3$^{f/f}$ mice showed less total distance (C) but comparable percentage of center distance (D) and center time (E) in the open field test; F-H: SST-Cre:AC3$^{f/f}$ mice exhibited decreased total arm entries (F), open arm time (G) and percentage of open arm entries (H) in the elevated plus maze test. Bars represent the mean ± standard error of the mean. Data were analyzed using one-way analysis of variance followed by post hoc Tukey's multiple comparisons test. n = 12 for AC3$^{flox/flox}$ group, n = 8 for SST-Cre group, n = 15 for SST-Cre:AC3$^{f/f}$ group. $^aP < 0.05$ *vs* AC3$^{flox/flox}$. $^bP < 0.01$ *vs* AC3$^{flox/flox}$. $^cP < 0.01$ *vs* SST-Cre. $^dP < 0.05$ *vs* SST-Cre. $^eP < 0.001$ *vs* SST-Cre.

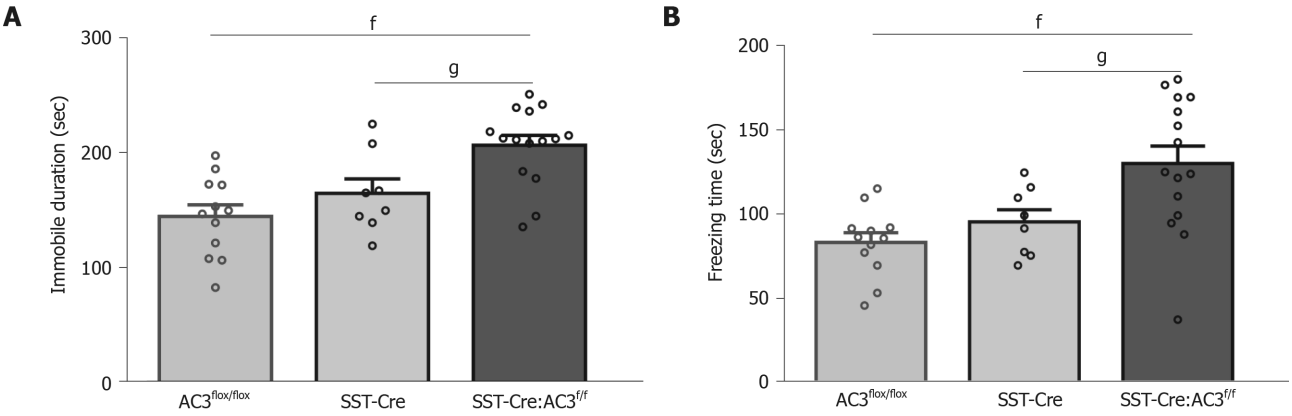
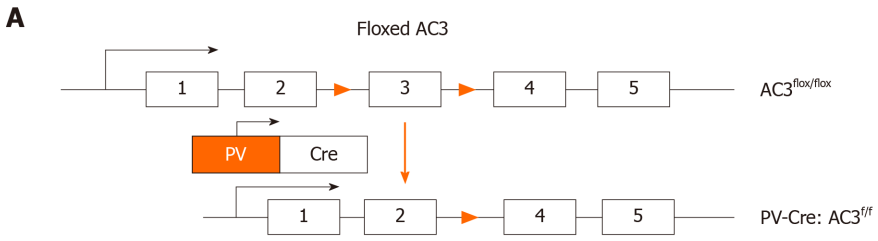


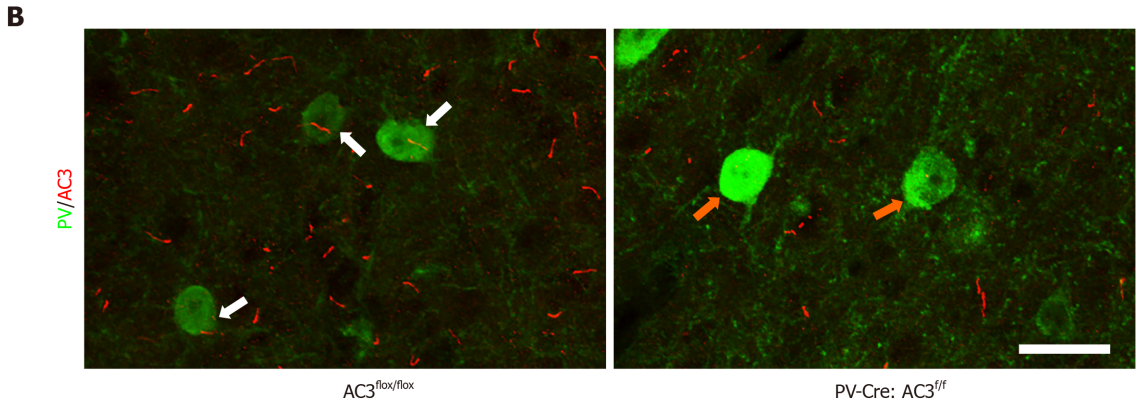
Figure 4 Somatostatin-Cre recombinase:type 3 adenylyl cyclase$^{f/f}$ mice showed depression-like behavior. A and B: Somatostatin-Cre recombinase (SST-Cre):type 3 adenylyl cyclase (AC3)$^{f/f}$ mice showed increased immobile duration in forced swimming test (A) and more freezing time in tail suspension test (B). Bars represent the mean ± standard error of the mean. Data were analyzed using one-way analysis of variance followed by post hoc Tukey's multiple comparisons test. n = 12 for AC3$^{flox/flox}$ group, n = 8 for SST-Cre group, n = 15 for SST-Cre:AC3$^{f/f}$ group. $^fP < 0.001$ *vs* AC3$^{flox/flox}$. $^gP < 0.05$ *vs* SST-Cre. .

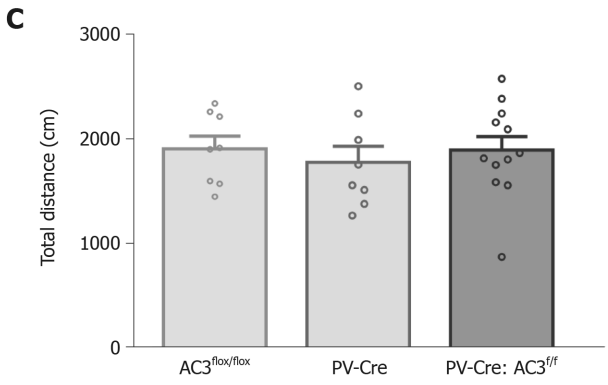
DISCUSSION

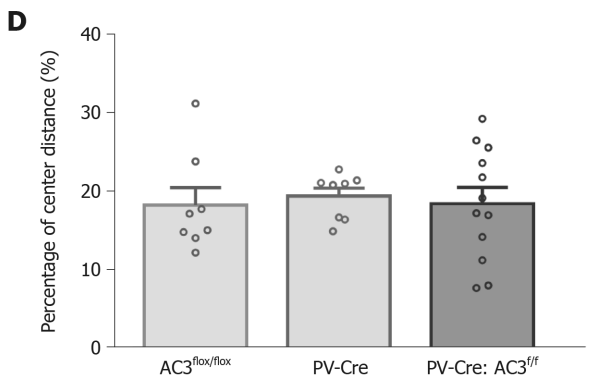
In this study, we determined if deletion of AC3 expression in two major GABAergic interneurons increases anxiety- and depression-related behaviors in mice. Our results indicated that the majority of SST$^+$ and PV$^+$ interneurons express AC3. Selective ablation of AC3 in SST$^+$ but not PV$^+$ interneurons induced anxiety- and depression-like behaviors, suggesting that loss of AC3 in the SST$^+$ interneurons may play an important role in the development of anxiety and depression in humans.

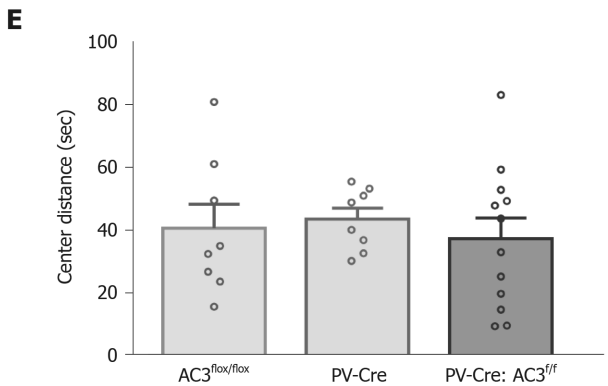
The balance between excitation and inhibition of neuronal circuit in the brain is interrupted in several neuropsychiatric disorders including MDD[7]. Recent evidence has shown that a deficit of inhibitory synaptic transmission contributes to the pathophysiology and development of MDD. Two major GABAergic interneurons, SST$^+$ and PV$^+$ cells, are subjects of interest in MDD. SST$^+$ interneuron synapses on the dendritic tufts of the nearby pyramidal neurons and is critical for gating the pattern of functional connectivity inputs[32]. In contrast to SST$^+$ interneurons, PV$^+$ GABAergic interneurons mainly target the soma of pyramidal neurons, thereby regulating action potential firing and promoting synchronization of electrical activity[33]. So, it is perhaps not so surprising that these two types of GABAergic interneurons play specific roles in different kinds of psychiatry disorders owing to their distinct electrical, neurochemical

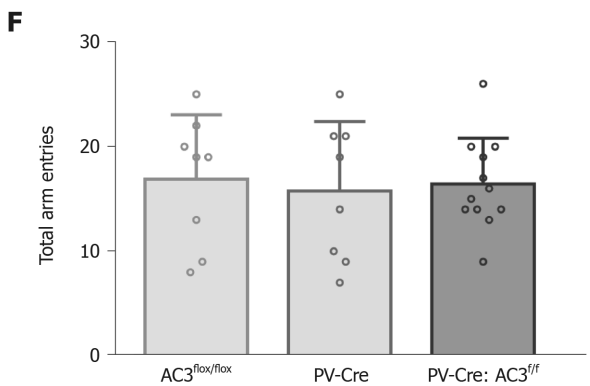

A
Floxed AC3
1
2
3
4
5
AC3flox/flox
PV
Cre
1
2
4
5
PV-Cre: AC3f/f


B
PV/AC3
AC3flox/flox
PV-Cre: AC3f/f


C
Total distance (cm)
3000
2000
1000
0
AC3flox/flox
PV-Cre
PV-Cre: AC3f/f


D
Percentage of center distance (%)
40
30
20
10
0
AC3flox/flox
PV-Cre
PV-Cre: AC3f/f


E
Center distance (sec)
100
80
60
40
20
0
AC3flox/flox
PV-Cre
PV-Cre: AC3f/f


F
Total arm entries
30
20
10
0
AC3flox/flox
PV-Cre
PV-Cre: AC3f/f

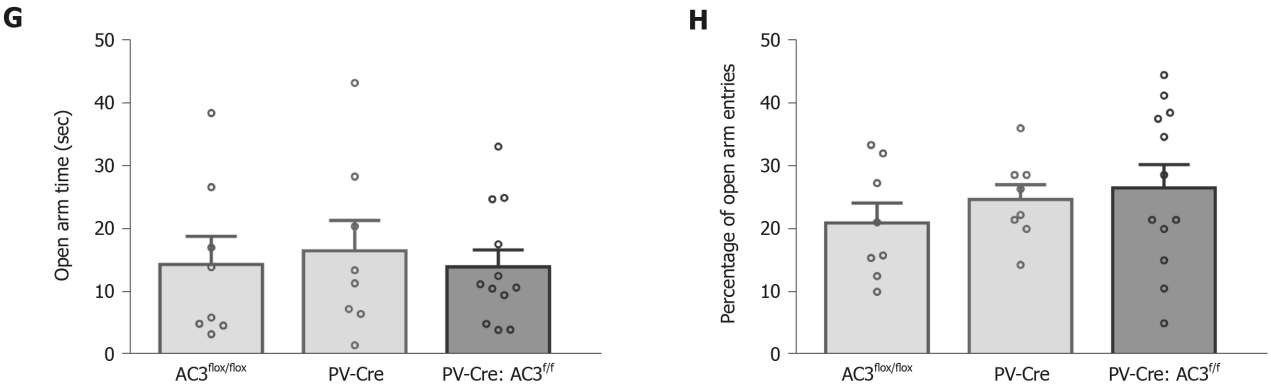


Figure 5 Parvalbumin-Cre recombinase:type 3 adenylyl cyclase$^{f/f}$ mice did not show anxiety-like behavior. A: Strategy for generation of parvalbumin-Cre recombinase:type 3 adenylyl cyclase$^{f/f}$ (PV-Cre:AC3$^{f/f}$) mice in which AC3 was selectively deleted in PV^{+} interneurons; B: Double immunohistochemistry showing the representative micrographs of AC3 protein expression (red) in PV^{+} interneurons (green) from AC3$^{flox/flox}$ control mice (left) and PV-Cre:AC3$^{f/f}$ mice (right). Solid arrows indicated that PV^{+} interneurons have well colocalization with AC3 in AC3$^{flox/flox}$ control mice. Empty arrow indicates that AC3 immunostaining disappeared in PV^{+} interneurons in PV-Cre:AC3$^{f/f}$ mice. Scale bar: 20 μm; C-E: Showing PV-Cre:AC3$^{f/f}$ mice showed similar total distance (C), percentage of center distance (D) and center time (E) in the open field test to control group; F-H: PV-Cre: AC3$^{f/f}$ mice exhibited comparable total arm entries (F), open arm time (G) and percentage of open arm entries (H) in elevated plus maze test compared with AC3$^{flox/flox}$ mice and PV-Cre mice. Bars represent the mean ± standard error of the mean. Data were analyzed using one-way analysis of variance followed by post hoc Tukey's multiple comparisons test. *n* = 8 for AC3$^{flox/flox}$ group, *n* = 8 for PV-Cre group, *n* = 12 for PV-Cre:AC3$^{f/f}$ group.

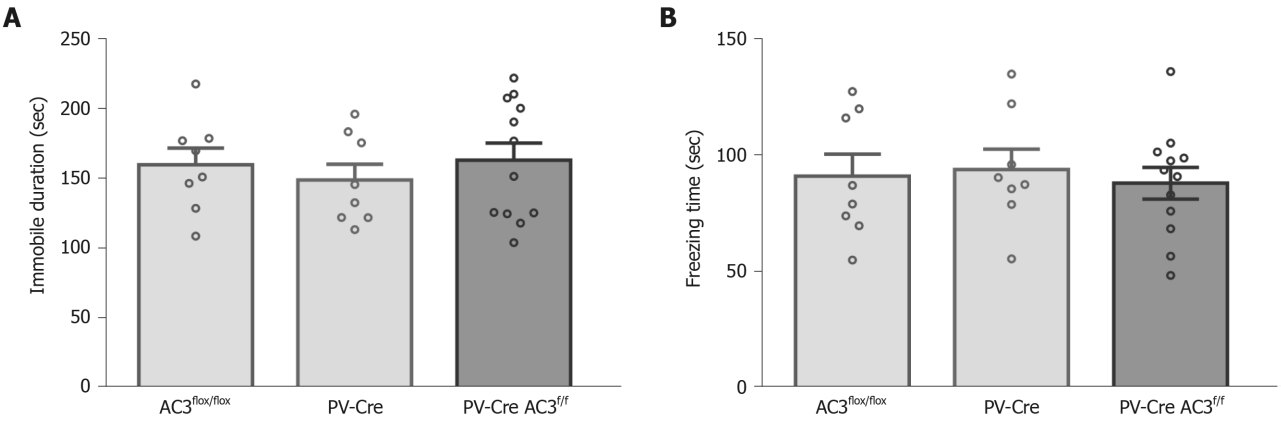


Figure 6 PV-Cre:AC3$^{f/f}$ mice did not show depression-like behaviors in the forced swimming test (A) and tail suspension test (B). Bars represent the mean ± standard error of the mean. Data were analyzed using one-way analysis of variance followed by post hoc Tukey's multiple comparisons test. *n* = 8 for type 3 adenylyl cyclase (AC3)$^{flox/flox}$ group, *n* = 8 for the parvalbumin-Cre recombinase (PV-Cre) group, *n* = 12 for the PV-Cre:AC3$^{f/f}$ group.

and structural properties. Our study indicates that the mice with selective ablation of AC3 from SST^{+} but not PV^{+} interneurons showed an anxiety- and depression-like behaviors, supporting the notion that specific subpopulation of GABAergic interneurons are functionally different. Our data are also consistent with several previous findings. For example, studies of brain samples from MDD corpses found that SST neurons were significantly attenuated and that expression of SST mRNA was reduced in multiple brain areas[14,34]. However, less obvious changes in PV^{+} interneurons in MDD patients were reported[18-20] although a reduced SgACC PV expression has been reported[21]. Moreover, contributions of SST^{+} but not PV^{+} interneurons to the pathophysiology of MDD has been directly supported through genetic and pharmacological manipulations in rodents. SST global knockout mice showed increased anxiety- and depression-like behaviors, elevated corticosterone level and decreased expression of BDNF, GAD67 and cortistatin genes expression[17]. However, selective activation of PV^{+} interneurons in the dentate gyrus of the hippocampus did not affect depression-like behavior in the TST[35]. Furthermore, mice with reduced BDNF expression (heterozygous deletion of BDNF gene [BDNF$^{+/-}$] or targeted disruption of exon IV [BDNF^{KIV}]) exhibited depressive-like behaviors and a robust and significant decrease of SST but not changes in PV expression[21]. Taken collectively, these previous studies and ours strongly indicated that central SST^{+} interneurons, as one type of susceptible GABAergic interneurons during MDD,

participated in the pathophysiology of anxiety- and depression-related disorders.

Previous studies from mice and humans have suggested a role for deficiencies in adenylyl cyclase and cAMP in depression and antidepressant responses[36,37]. However, the relationship with adenylyl cyclase and depression is more complex because of the diversity of adenylyl cyclase isoforms. A notable finding of present study is that SST-Cre:AC3$^{f/f}$ mice produced anxiety- and depression-like behaviors after selective disruption of AC3 in SST$^+$ interneurons, suggesting that reduction of AC3 expressed in SST$^+$ interneurons may contribute to MDD. The data in this study is also confirmed with our previous studies showing that disruption of AC3 gene globally, conditionally, or targeted to forebrain caused depression-like behaviors in transgenic mice[30]. We do not know why loss of AC3, which is expressed in the primary cilia of CNS neurons, caused depression in mice. However, ablation of type III adenylyl cyclase in mice causes reduced neuronal activity and altered sleep patterns[30]. This suggests the interesting possibility that the depression-like behavior seen with AC3$^{-/-}$ mice might be caused by a chronically decreased SST$^+$ neuronal excitability, subsequently impairment of GABAergic inhibitory synaptic input from SST$^+$ interneurons to pyramid cells, which is consistent with the GABAergic deficit hypothesis of MDD.

CONCLUSION

In summary, primary cilia in SST$^+$ interneurons may sense extracellular signals through non-synaptic transmission and transduce it into the neurons. Then the cellular signals may regulate by AC3 in primary cilia and effect on the activity of SST$^+$ interneurons. The changes in SST$^+$ interneurons may further affect the downstream neurons and modulate anxiety- and depression-like behaviors in mice.

ARTICLE HIGHLIGHTS

Research background

Major depressive disorder (MDD) is a highly disabling and phenotypically heterogeneous psychiatric syndrome that is among the leading contributors to social and economic burden.

Research motivation

Studies from patients and animal models suggest a key role for functional imbalances between the excitatory and inhibitory neurotransmitters in the central nervous system. Somatostatin-positive (SST$^+$) and parvalbumin-positive (PV$^+$) neurons are two major GABAergic interneurons and play roles in excitation/inhibition balance. Type 3 adenylyl cyclase (AC3) has been reported as a top-ranked gene in MDD and our previous study indicated that AC3 globally knockout mice showed depression-like behaviors. We hope to know whether AC3 in these two subtypes of interneurons contributes to the pathophysiological process of depression.

Research objectives

To determine whether ablation of AC3 gene in different subtypes of GABAergic interneurons of mice produces depression-like behaviors.

Research methods

Immunohistochemistry, genetic manipulations, and a series of behavior tests were used in this study.

Research results

We found that selective disruption of AC3 in SST$^+$ but not PV$^+$ interneurons caused anxiety- and depression-like behaviors.

Research conclusions

AC3 in SST$^+$ interneurons play a key role in the etiology of depression.

Research perspectives

The AC3-dependent molecular mechanisms in SST$^+$ interneuron underlying MDD will

be further explored.

ACKNOWLEDGEMENTS

We thank Dr. Qin GY for the biostatistics check.

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World Journal of Psychiatry

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World J Psychiatr 2021 February 19; 11(2): 50-57

DOI: 10.5498/wjp.v11.i2.50

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

Psychic euosmia among obsessive-compulsive personality disorder patients: A case control study

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Institutional review board statement: The study was reviewed and approved by the Policlinico Umberto I Institutional Review Board, approval No. 6080.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Abstract

BACKGROUND

Psychic euosmia (PE) has been described as a supposed psychological predisposition for which pleasant smells elicit an immediate sense of pleasure, order and calmness in obsessive-compulsive personality disorder (OCPD). In this study we tried to verify the interpretation that PE is the counterpart of disgust that has been associated to contamination and moral purity. Disgust and morality are significantly associated in people with obsessive-compulsive personality traits. We expected that OCPD patients would experience higher levels of PE.

AIM

To investigate the PE frequency in OCPD patients and healthy controls (HC) and to evaluate the relationship between PE and disgust.

METHODS

A single-center, case-control study was conducted in an outpatient service for obsessive-compulsive and related disorders. The sample consisted of 129 subjects: 45 OCPD patients and 84 HC. In both groups we submitted the Disgust Scale Revised (DS-R) and the self-report Structured Clinical Interview for DSM-5 Screening Personality Questionnaire to which we added an additional yes or no

Conflict-of-interest statement: All authors declare the absence of conflict of interests related to the present study.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Manuscript source: Unsolicited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: September 17, 2020
Peer-review started: September 17, 2020
First decision: December 1, 2020
Revised: December 13, 2020
Accepted: December 27, 2020
Article in press: December 27, 2020
Published online: February 19, 2021

P-Reviewer: Liu C, Vyshka G
S-Editor: Huang P
L-Editor: Filipodia
P-Editor: Li JH

question to investigate the presence of PE. In order to verify differences between groups, *t*-test was employed for continuous variables and ^{2} test for categorical variable; odds ratio was employed to analyze group differences in the PE survey. Correlation was explored with Pearson *r* correlations.

RESULTS

No differences were observed between groups in gender composition or education. A slight significant difference was found in mean age (t = 1.988; P = 0.049). The present study revealed significantly higher proportions of PE among OCPD patients when compared to HC (OR: 5.3, 2.28-12.46). Patients with OCPD were more likely to report PE (n = 36; 80%) whereas a much lower proportion endorsed PE in the HC group (n = 36; 42.9%). Interestingly, no differences were observed between groups in mean score for the Disgust Scale. There was also no difference between the two groups in any of the Disgust Scale Revised subscales. Moreover, no significant correlations were observed in the OCPD group between PE and Disgust Scale Revised subscales.

CONCLUSION

Results suggested that PE might be part of the clinical spectrum of OCPD, and it does not reflect the counterpart of disgust. This could also indicate that this phenomenon is a manifestation of orderliness or incompleteness. Further studies will need to be undertaken to better understand PE and its significance in OCPD.

Key Words: Psychic euosmia; Obsessive-compulsive personality disorder; Disgust; Orderliness; Olfactory; Personality

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Core Tip: Psychic euosmia (PE) is a positive aspect of obsessive-compulsive personality disorder (OCPD) recently described as a psychological predisposition for which pleasant smells elicit an immediate sense of pleasure, order and calmness. In the absence of other scientific observations, our group decided to investigate the presence of this phenomenon among OCPD patients and how PE ought to be considered. The present study revealed significantly higher rates of PE among OCPD patients compared to healthy control subjects. The absence of correlation between PE and the Disgust Scale in the OCPD group supports the hypothesis that this experience is not associated with disgust.

Citation: Maraone A, Tarsitani L, Frascarelli M, Petrini F, Roselli V, Tinè M, Cavaggioni G, Brakoulias V, Biondi M, Pasquini M. Psychic euosmia among obsessive-compulsive personality disorder patients: A case control study. *World J Psychiatr* 2021; 11(2): 50-57
URL: https://www.wjgnet.com/2220-3206/full/v11/i2/50.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i2.50

INTRODUCTION

Obsessive-compulsive personality disorder (OCPD), also known as anankastic personality disorder in the ICD-11[1], is one of the most represented personality disorders in the general population with a prevalence ranging from 2.1% to 7.9%[2-4]. OCPD has a high comorbidity with obsessive-compulsive disorder (OCD), with a rate ranging from 23% to 47%[5-9] as well as body dysmorphic disorder[10,11], autism spectrum disorder[12,13] and eating disorders[14,15]. The high rates of comorbidity have led researchers to speculate that OCPD bears a relationship with OCD[16]. Janet[17] described the manifestations and the core traits of OCPD, referring to particular aspects of "psychoasthenia," such as excessive controlled emotional expression, inability to achieve perfection, indecisiveness, orderliness and stubbornness. Later, Lewis[18] described two types of personalities in persons with OCPD: One characterized by negative affect, stubbornness and irritability and the other by uncertainty and submissiveness. During the years, the description of OCPD has evolved and is

currently defined by the DSM-5 as "a pervasive preoccupation for orderliness, perfectionism, mental and interpersonal control at the expense of flexibility, openness and efficiency"[2]. At the same time, the DSM-5 coded OCD in a new taxonomy called obsessive-compulsive and related disorders (OCRD). As reported by Fineberg *et al*[16], OCPD is typically associated with a restricted repertoire of rigid, stereotyped and disabling compulsive thinking patterns and behaviors with attaining completeness and intra- and interpersonal control, like doubting, checking and hoarding, are experienced as ego-syntonic or rather perceived as appropriate and correct by the person affected. Moreover, the same authors suggest the overlap of several characteristics between OCPD and OCD support the inclusion of OCPD in the OCRDs.

Thus, Riddle *et al*[19] described two specific dimensions in OCPD patients: One characterized by order and control and the other by hoarding and indecision. According to a dimensional approach, personality disorders can be considered "a quantitative" variation of personality traits, within a continuum between normality and psychopathology. In this sense, some manifestations such as orderliness and cleanliness in OCPD subjects do not necessarily represent a maladaptive variant. Few studies have focused on positive aspects of OCPD[20].

Psychic euosmia (PE)[21] is a positive aspect of OCPD that was recently described as a psychological predisposition for which pleasant smells elicit an immediate sense of pleasure, order and calmness in OCPD. In the absence of other scientific observations, our group decided to investigate the presence of this phenomenon among OCPD patients and subsequently how PE ought to be considered. We delineate three possible hypotheses: PE is a manifestation of orderliness, is a just right component or is the counterpart of disgust that has been associated with contamination and moral purity. In this study we tried to verify this last interpretation. Accordingly, Ottaviani *et al*[22] supported the relationship between disgust and morality, which are significantly associated in people with obsessive-compulsive personality traits. It is possible to distinguish core disgust, elicited by different physical stimuli, and moral disgust, specifically human, induced by immoral behavior that violates justice and human dignity[23]. Disgust involves the autonomic nervous system; several studies showed neurovegetative equivalents, like nausea and changes in the normal rhythm of stomach contractions and fainting, were associated with changes in the cardiovascular system during disgust by activation of the vagus nerve[24-26]. Neuroimaging studies reported activation of brain areas implicated in the emotion of disgust, such as the insula. The insula has been strongly implicated in perceiving and experiencing different forms of disgust[27,28].

The present study aimed at evaluating the presence of PE in a group of patients with a diagnosis of OCPD without comorbidity compared with healthy controls (HC). We expected that OCPD patients would experience higher levels of PE. The second aim was to ascertain the possible relationship between PE and disgust.

MATERIALS AND METHODS

To investigate whether the frequency of PE differs in patients with OCPD and HC and whether this component is related to disgust, we conducted a case-control study in consecutive outpatients enrolled in 2019 at an outpatient service for OCRDs, Policlinico Umberto I, Rome. The study was conducted in agreement with the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all eligible participants following a complete description of study details. Participants were informed regarding their freedom to withdraw from the study at any time without any negative effect on their therapy. The sample consisted of 129 subjects: 45 patients affected by OCPD and 84 HC. HC were recruited through "word of mouth" among volunteers. All participants were assessed for the presence of a psychiatric disorder with clinical interview using the diagnostic criteria based on the DSM-5[2]. Both the HC subjects and the cases were assessed by the same trained personnel. Having comorbidity psychiatric diagnosis and/or cognitive impairment was considered an exclusion criterion. From an initial sample of 52 patients diagnosed with OCPD, 7 subjects were excluded from the analysis due to comorbidity with OCD. Demographic data were collected for all samples. To explore the presence of OCPD in both groups, we submitted self-report Structured Clinical Interview for DSM-5 Screening Personality Questionnaire[29] to which we added an additional question, derived from the most common unsolicited affirmation of patients regarding this phenomenon, to investigate the presence of PE: "Do you happen to feel an immediate sense of well-being, or be in a good mood all of a sudden, or feel

calmness as soon as you smell clean or fresh smells (like fresh laundry)? Give us some examples."

The common unsolicited affirmation of patients often refers to a prompt mood improvement upon encountering good scents in general, or fresh laundry borax on their clothes, pillows or home settings. We have asked for examples in order to verify if subjects' answers were congruent with the framework of PE.

Moreover, all participants completed the Disgust Scale Revised (DS-R) to evaluate the disgust sensitivity. We used the Italian version[30] of DS-R[31,32]. This version is a self-report questionnaire that includes 25 items describing stimuli that elicit disgust across three distinct domains: Core disgust, animal-reminder disgust and contamination-based disgust. The scale is divided into two sections, and each section presents items for each domain. There are 13 items plus 1 trick question in the first section and 12 items plus 1 trick question in the second section. All items are rated on a 5-point scale from 0 (strongly disagree/not disgusting at all) to 4 (strongly agree/extremely disgusting). The total scale score is the sum of the 25 items, after reversing the scores for items 1, 6 and 10.

Statistical analysis was performed with SPSS 24 (IBM) software. In order to verify differences between groups, *t*-test was employed for continuous variables and χ^2 test for categorical variable. In order to verify differences between groups in the presence of PE, the odds ratio and its 95% confidence level according to the Woolf's method were calculated[33]. Correlation between variables was explored with Pearson *r* correlations. Bonferroni correction for multiple comparisons was applied. Statistical review of the study was performed by a biomedical statistician. The statistical methods of this study were reviewed by Pasquini P, MD, MPH, former Head of Department of Epidemiology and Biostatistics at Istituto Superiore di Sanità, Rome, Italy.

RESULTS

Socio-demographic characteristics of the subjects are shown in Table 1. No differences were observed between groups in gender composition or education. A significant difference was found in mean age as the patient group was older than the HC (P = 0.049). Regarding the presence of PE, significant differences were found between groups in how they answered the corresponding item during the interview (OR 5.34, 2.28-12.46) (Table 2). Among our 45 study subjects with OCPD, 36 (80%) were positive, while among 84 HC only 36 (42.9%) were positive. Interestingly, no differences were observed between groups in mean score on the Disgust Scale (t = 1.298; P = 0.197). There was also no difference between the two groups in the DS-R subscales (Table 3). No significant correlations were observed in the OCPD group between PE and DS-R subscales.

DISCUSSION

The present study revealed significantly higher proportions of PE among OCPD patients when compared to HC subjects. Thereby meaning that PE might be part of the clinical spectrum of OCPD. We also found that there were no significant differences in disgust sensitivity between OCPD patients and HC. Moreover, the absence of correlation between PE and subscales of Disgust Scale in OCPD group supported the hypothesis that this experience was not associated with disgust in this population.

This finding suggests that PE does not reflect the counterpart of disgust and might also indicate that this phenomenon is a manifestation of orderliness or incompleteness. Indeed, the sense of calmness derived by an experience of a pleasant smell would seem to complete the sense of perfection in an otherwise uncomfortable person. This might suggest that PE could be a manifestation of incompleteness. According to the dimensional approach, such maladaptive variants of personality disorder traits could transition imperceptibly into a spectrum of normal[16,34]. The same could be true for adaptive traits. As an example, in a normalcy *vs* pathology continuum approach, being conscientious or a tendency to be orderly and well organized may resemble a normal condition with several advantages in certain situations. Not surprisingly few studies have focused on positive aspects of OCPD[35]. On the other hand, PE could be conceptualized as a normal reaction.

A strength of our study is that comorbidity was excluded. However, our study is limited in that the sample size was small, we did not examine a second control group composed of patients affected by other psychiatric disorders, and we only interviewed

Table 1 Socio-demographical characteristics of the sample

Variable	HC, *n* = 84	OCPD, *n* = 45	Statistics	
	mean ± SD	mean ± SD	*t*	*P* value
Age	38.9 ± 15.2	44.9 ± 17.3	1.988	0.049
Education in yr	15.9 ± 2.7	15.3 ± 3.1	1.103	0.272
Sex	***n* (%)**	***n* (%)**	$\chi 2$	***P* value**
Male	36 (42.9)	21 (46.7)	0.233	0.629
Female	48 (57.1)	24 (53.3)		

[a]$P < 0.05$.

HC: Healthy controls; OCPD: Obsessive-compulsive personality disorder; SD: Standard deviation.

Table 2 Estimated odds ratio for the presence of psychic euosmia

	OCPD, *n*	HC, *n*
Presence of PE	36	36
Absence of PE	9	48

HC: Healthy controls; OCPD: Obsessive-compulsive personality disorder; PE: Psychic euosmia.

Table 3 Mean scores and standard deviation in each Disgust Scale Revised subscale

Disgust Scale-Revised subscales	OCPD, *n* = 45	HC, *n* = 84	Statistics	
	mean ± SD	mean ± SD	*t*	*P* value
Core	28.2 ± 8.5	27.2 ± 8.2	0.692	0.490
Animal reminder	16.0 ± 6.7	14.6 ± 6.5	1.140	0.257
Contamination	9.2 ± 4.9	7.8 ± 3.5	1.765	0.082
Total	53.5 ± 17.3	49.6 ± 15.6	1.298	0.197

HC: Healthy controls; OCPD: Obsessive-compulsive personality disorder.

help-seeking patients attending an outpatient clinic for OCRD. This may have biased our sample. To the best of our knowledge, this is the first case-control study on PE. There is need for additional research to better understand PE and its significance in OCPD.

CONCLUSION

Results suggest that PE might be part of the clinical spectrum of OCPD, and it does not reflect the counterpart of disgust. In our study, PE is over-represented among OCPD subjects. This supports an association, and one might speculate that PE is related to orderliness and cleanliness in this population. Using an evolutionary hypothesis, PE may reflect one's ability to differentiate between unpleasant and pleasant odors, which may have made a difference in terms of survival or death[36].

ARTICLE HIGHLIGHTS

Research background

According to a dimensional approach, personality disorders can be considered "a

quantitative" variation of personality traits within a continuum between normality and psychopathology. In this sense, some manifestations such as orderliness and cleanliness in obsessive-compulsive personality disorder (OCPD) subjects do not necessarily represent a maladaptive variant. Psychic euosmia (PE) is a positive aspect of OCPD that was recently described as a psychological predisposition for which pleasant smells elicit an immediate sense of pleasure, order and calmness in OCPD.

Research motivation

Few studies have focused on positive aspects of OCPD. In the absence of other scientific observations, our group decided to investigate the presence of this phenomenon among OCPD patients and subsequently how PE ought to be considered.

Research objectives

We delineate three possible hypotheses: PE is a manifestation of orderliness, is a just right component, or is the counterpart of disgust that has been associated to contamination and moral purity. In this study we tried to verify this last interpretation.

Research methods

The sample consisted of 129 subjects: 45 patients affected by OCPD and 84 healthy controls. To explore the presence of OCPD in both groups we submitted self-report Structured Clinical Interview for DSM-5 Screening Personality Questionnaire to which we added an additional question to investigate the presence of PE. All participants completed the Disgust Scale Revised to evaluate the disgust sensitivity. We used the Italian version of the Disgust Scale Revised.

Research results

Regarding the presence of PE, a significant difference was found between groups in how they answered the corresponding item during the interview. Among the 45 study subjects with OCPD, 36 (80%) were positive. While among 84 HC, only 36 (42.9%) were positive. Interestingly no differences were observed between groups in the mean score at the Disgust Scale.

Research conclusions

Results suggest that PE might be part of the clinical spectrum of OCPD, and it does not reflect the counterpart of disgust. In our study, PE is over-represented among OCPD subjects. This supports an association, and one might speculate that PE is related to orderliness and cleanliness in this population.

Research perspectives

To the best of our knowledge, this is the first case-control study on PE. There is need for additional research to better understand PE and its significance in OCPD.

ACKNOWLEDGEMENTS

The authors wish to thank all the patients and healthy controls participating in the study.

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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 March 19; 11(3): 58-86



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Production Editor: *Jia-Hui Li*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
March 19, 2021

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World J Psychiatr 2021 March 19; 11(3): 58-62

DOI: 10.5498/wjp.v11.i3.58

ISSN 2220-3206 (online)

ETHICS

Rapid commentary: Ethical implications for clinical trialists and patients associated with COVID-19 research

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Author contributions: Delanerolle G, Phiri P and Raymont V made significant contribution to the development of the draft; Delanerolle G, Phiri P, Raymont V, Elliot K, Ramakrishnan R, Rathod S, Thayanandan T, Sandle N and Haque N contributed to the manuscript revisions and approved the final version.

Conflict-of-interest statement: Phiri P has received research grant from Novo Nordisk, and other, educational from Queen Mary University of London, other from John Wiley & Sons, other from Otsuka, outside the submitted work. Rathod S reports other from Janssen, Lundbeck and Otsuka outside the submitted work. All other authors report no conflict of interests for this article. The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, the Department

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Abstract

Pandemics disrupt clinical trials worldwide, with lasting effects on research. It can severely impact clinical trialists ability to conduct safe and ethically uncompromised trials. Hence, the mounting pressure results in ethically and morally distressing decisions faced by clinical trial professionals during pandemic situations. Whilst clinical trialists attempt to think about preparedness and responses during a pandemic, the need to have an ethical framework that has real-world applicability is imperative. Pandemics are a challenging time for all, however, the safety and access to support for clinical trialists and patients within clinical trials should be at the forefront for their organisations and the government.

Key Words: COVID-19; Pandemic; Ethics; Clinical trials; Patients; Trialists

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Core Tip: This commentary provides an important facet and argues the ethical implications surrounding clinical research practices and staff during pandemic

situations. Clinical trial professionals face ethical dilemmas whilst conducting trials safely at an unprecedented rate given the clinical urgency. This commentary highlights the detrimental impact of not having a protocol for pandemic-driven clinical research, as well the lack of an ethical framework with *real-world* applicability to support the clinical trial workforce. Unethical behaviours and practices could be introduced in the current pressurised climate in order to rapidly respond to coronavirus disease 2019 research in particular.

Citation: Delanerolle G, Rathod S, Elliot K, Ramakrishnan R, Thayanandan T, Sandle N, Haque N, Raymont V, Phiri P. Rapid commentary: Ethical implications for clinical trialists and patients associated with COVID-19 research. *World J Psychiatr* 2021; 11(3): 58-62
URL: https://www.wjgnet.com/2220-3206/full/v11/i3/58.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i3.58

INTRODUCTION

A pandemic is a time to focus on containing the clinical situation, ensuring deaths are minimised, reviewing the causation and developing treatments. However, the ethical implications surrounding clinical research practices and staff may be less considered. Ethically and morally distressing decisions maybe faced by many clinical trial professionals during pandemic situations. These decisions, which could be seen as "moral injury", may impact upon an individual's ethical and moral code and may develop into feelings of shame and guilt[1]. In the current coronavirus disease 2019 (COVID-19) pandemic, the wider psychosocial and psychological impact of the pandemic amongst Clinical Trialists is yet to be explored. Whilst there is an argument that there could be personal factors that may contribute to this, Clinical Trialists have had to reprioritise their work regimes to deliver research around severe acute respiratory syndrome coronavirus 2.

A useful document that has aided Clinical Trialists in particular is the World Health Organisation's (WHO) pandemic preparedness document. Interestingly the National Institute for Health Research also provided guidance and paused non-COVID related research as of March 20, 2020. The WHO's pandemic preparedness framework was a result of a workshop conducted in 2018 amongst the Global Health Ethics Team and the African coaLition for Epidemic Research, Response and Training. The purpose of this workshop was to discuss and identify empirical processes and procedures in relation to ethics reviews and preparedness during pandemics. This included five key areas in particular; pre-review of study protocols (including multi-country reviews), coordination between national ethics committees, statistical and stakeholder considerations, data and outcome sharing, as well as transfer of samples to share knowledge and develop future proofed interventions. Another key development to come out of this workshop were standard operating procedures (SOPs) for ethical reviews, in part to protect staff and their time while conducting pandemic research. These SOPs were to provide clarity on terminology and expectations of the pre-review of protocols and to agree a specific set of standards to speed up the process. Whilst these recognised a number of complex ethical issues could be raised during pandemics, it is also imperative to consider both research and clinical staff resources. Various other aspects such as quality assurance, regulatory requirements and operational delivery of the required research, which arguably could have ethical implications due to the by-stander effect this generates, were not well discussed and reported. This should be a fundamental aspect to consider with any future pandemic preparedness documentations as well as any associated procedures. Additionally, ethical implications for specific staff groups should be considered, to ensure policy makers are able to develop relevant guidelines.

Ethical implications associated with pandemics have significantly evolved over the centuries, but developing fit for practice ethical guidelines universally applicable to policy makers, healthcare systems and clinical trial units appears to have been challenging. Furthermore, ethical implications and principles may be driven by the pandemic itself. A good example would be to consider research conducted during the H5N1 influenza endemic. A significant limitation with H5N1 research was that longitudinal data was scarce and so its wider use and applicability was constrained. In

of Health and Social Care or the Academic institutions.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United Kingdom

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 15, 2020
Peer-review started: December 15, 2020
First decision: January 7, 2021
Revised: January 28, 2021
Accepted: March 8, 2021
Article in press: March 8, 2021
Published online: March 19, 2021

P-Reviewer: Gallo G
S-Editor: Fan JR
L-Editor: A
P-Editor: Li JH

order to aid future pandemic management plans or to better understand transmission of a virus on the scale of a pandemic, existing data could have been used as part of prediction model, to support research staff. Whilst, the infection was managed in various ways, clinical trial staff had a different set of ethical considerations that were needed to have been addressed. Currently, there is no evidence to suggest these ethical considerations for trial staff were explored and reported. The vulnerability in this situation, of course, is that addressing the needs of a pandemic alongside the need for clinical research to develop treatments and vaccines, has to sit alongside access to care and the ethical obligations of research and to our clinical research staff.

IMPACT OF PANDEMIC RESEARCH ON CLINICAL TRIALISTS

All clinical trials testing licensed or unlicensed drugs and vaccines are mainly led by clinicians and clinical academics and there are staff from many disciplines working as Clinical Trialists. Therefore, the research associated with a pandemic, resourcing levels and the mental and physical impact varies considerably. Whilst there is a wide acceptance resource issues in the NHS, this has been exacerbated during the current pandemic. As a result, there appears to have been a heavy reliance on clinical and non-trial staff to deliver some clinical trials, which could impact their mental wellbeing in the long term, although this hypothesis would require further investigation.

Interestingly, Alperovitch and colleagues[2] stipulated whilst there is a need for research to be conducted during a pandemic, the major implications are in respect to managing the ethical principles pertaining to the studies themselves, research participants and Clinical Trialists. A key issue to consider is the informed consent aspect. Some studies have had deferred and/or waived consent models when conducting clinical trials during previous pandemics[2]. Whilst participants, clinicians and researchers often agree emergency research consent could be waived in some urgent situations, this method isn't suitable and acceptable for all. Clinical Trialist based research requires informed consent, and recognition that an electronic method of conducting a trial could be an efficient way to gather insightful data to further evaluate this is often missed. For example, the European Medicines Agency has provided clarity that informed consent must be taken before enrolling any patients into COVID-19 clinical trials taking place in Europe. Gobat and colleagues[3] discussed this issue further in their systematic review, and highlighted that patients accept clinicians acting as surrogate arbitrators. However, research regulators were more judicious if studies had substitute consenting procedures. Also, while further recommendations around study setup and protocol design need to be fit for purpose for any pandemic-driven clinical research such research should comply with both research and practice ethics. Alternative consent models could also have major psychological impact on Clinical Trialists and research to this effect remains limited.

Balancing clinical care and research to manage pandemic preparedness

Another common ethical argument presented during pandemics is that clinical care for current patients outweighs clinical research around non-pandemic issues. This may impact both patients and ongoing clinical care in a multitude of ways. Currently there are clinical trials taking place to test the use of Lopinavir, Ritonavir or Dexamethasone for COVID-19 (*via* the RECOVERY Trial); all of which are licenced treatments for other diseases. As there is clinical and adverse effect data already available for these drugs, there are minimal risks and ethical and moral implications for staff conducting these trials, when compared with COVID-19 vaccine studies or first in human trials. However, there could be unlicensed drugs that may also be suited to combating a new infection or a modified strain of a known infection such as COVID-19.

Another facet to pandemic preparedness is whether countries have ample research capacity to ensure an efficient and effective response in terms of research. The requirement for ethical principles and merit of incorporating these into research and clinical practices using specific guidelines could be endorsed during public health emergencies and it is widely recognised this could be a cost effective way to further operational capacity for Clinical Trialists in particular. As such, policy makers, clinicians, researchers and stakeholders need to identify time and resources to provide immediate treatment and maintain other activities, inclusive of an integrated approach for research as part of a pandemic response. In situations such as the COVID-19 pandemic, developing research and clinical practice "ethics preparedness" can help provide an efficacious response.

Challenges with implementation

Whilst ethical preparedness has the potential to cover an array of factors, a key challenge is the applicability of ethical standards between the "individual" and "group". There may be conundrums around duty to act to preserve lives of patients and the general public, *vs* the personal risks of those providing clinical care. It is clear that those in frontline clinical positions put themselves at risk in order to save lives and that this is morally acceptable. However, there may be others who may feel, as a healthcare professional, their right to conduct their role in a safe manner is compromised due to the very obligations of the role they play during a pandemic.

Identifying specific risks for staff

COVID-19 has a unique aspect, that is, the infection having particular effects on the black, Asian and minority ethnic (BAME) population based on the current data reported specifically within the United Kingdom. 44% of the NHS workforce belongs to the BAME population and to date, several reports state approximately 62%-75% of the 181 healthcare worker deaths were of BAME descent[4-6]. Ethnicity has the potential to influence the disease transmission through societal, cultural and behavioural differences[7]. The Francis report[8] found the frontline doctors who are of ethnic minorities may feel more vulnerable to raising concerns at work, thus BAME staff may not have vocalised concerns around their health risks and lack of access to personal protective equipment (PPE) during the pandemic. Minimal or lack of PPE has been found to correlate with increased anxiety levels in healthcare professionals[1]. As the causation of the ethnic bias in COVID-19 is yet to be understood, this introduces ethical implications for those serving in the frontline and in COVID-19 related research and potentially needs further investigation before this impacts other frontline BAME staffing groups.

RISKS OF PREDICTION MODELS

Historically, the rate of deaths during a pandemic depends on the number of those infected, the virulence of the infection and the efficiency and effectiveness of the preventative measures[9]. In addition, accurate mortality rates can be challenging to establish. However, this may be because the use of Artificial intelligence (AI) methods, coupled with data science and its influence on healthcare, has been minimal until now. Therefore, another facet to complicate ethical implications for staff could be that prediction models for COVID-19 are AI instead of traditional statistics. Whilst, AI methods and statistics have their own strengths and weakness, the rapid reviews being conducted to develop these prediction models could lack quality and perhaps be poorly reported, which would contribute to increasing bias. This was highlighted in a recent systematic review conducted by Wynants and colleagues[10]. Therefore, there is an argument that unethical behaviours and practices could be introduced in the current pressurised climate due to the rapid response-based research conducted. Whilst conducting "rapid reviews" is very much appropriate and is a time sensitive matter, academia maybe overloading the journals with a large number of papers in a bid to put their views across and to support healthcare practitioners. This could raise more confusion within frontline services than anything else. In fact, this counter productivity itself could be deemed unethical. Furthermore, an already overstretched healthcare system may feel overwhelmed and may also have very limited time to use this evidence in a meaningful manner.

CONCLUSION

It is anticipated that national research ethics committees, research consortia, funding agencies, healthcare organisations and policy makers will work towards promoting better recommendations and for conducting effective research during a pandemic, whilst still protecting our clinical trial workforce. A key factor that must remain at the forefront as we think about preparedness and responses during a pandemic, is that, despite theoretical and conceptual debates, the real-world applicability of any ethical frameworks is imperative. This is vital to keep in mind when decisions are made with regard to research and supportive strategies for clinical research staff working during pandemics.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 March 19; 11(3): 63-72

DOI: 10.5498/wjp.v11.i3.63

ISSN 2220-3206 (online)

OPINION REVIEW

Exorcising memories of internalised stigma: The demons of lived experience

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Author contributions: The author prepared the ideas for the article herself and is the sole author.

Conflict-of-interest statement: There was no conflict of interest in the writing and publication of this article.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United Kingdom

Peer-review report's scientific quality classification

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Abstract

Public stigma and self-stigma impact negatively on the lives of people with mental health issues. Many people in society stereotype and discriminate against people with mental ill-health, and often this negative process of marginalisation is internalised by people with lived experiences. Thus, this negative internalisation leads to the development of self-stigma. In this article, I reflect on my own experiences of shame and self-stigma as a person with mental ill-health socially bullied by peers from my community and social groups. I present a personal narrative of both public and self-stigmatisation which I hope will enable me to exorcise memories of internalised stigma, which are encountered as my demons of lived experience. Using reflexivity, a process used widely in health and social care fields, I consider how social bullying shattered my fragile confidence, self-esteem, and self-efficacy in the early days of my recovery; the impact of associative stigma on family members is also explored. Following this, the potential to empower people who experience shame and stigma is explored alongside effective anti-stigma processes which challenge discrimination. I connect the concept of recovery with the notion of empowerment, both of which emphasise the importance of agency and self-efficacy for people with mental ill-health. Finally, I consider how the concepts of empowerment and recovery can challenge both the public stigma held by peers in the community and the self-stigma of those with lived experiences.

Key Words: Stigma; User-led narrative; Reflexivity; Empowerment; Recovery; Mental health

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Core Tip: The article explores the experiences of stigma and discrimination experienced

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 20, 2020
Peer-review started: December 20, 2020
First decision: January 7, 2021
Revised: January 14, 2021
Accepted: February 26, 2021
Article in press: February 26, 2021
Published online: March 19, 2021

P-Reviewer: Chakrabarti S, Kishor M
S-Editor: Zhang L
L-Editor: A
P-Editor: Li JH

by a person with lived experience of mental ill-health. It explores how both public stigma and self-stigma can shatter fragile confidence and impact negatively on both self-efficacy and self-esteem. Connections with the importance of empowerment and recovery in mental health are considered, and how they can overcome the sense of shame and self-pity experienced by people with mental ill-health who encounter social bullying by peers in their community.

Citation: Fox JR. Exorcising memories of internalised stigma: The demons of lived experience. *World J Psychiatr* 2021; 11(3): 63-72
URL: https://www.wjgnet.com/2220-3206/full/v11/i3/63.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i3.63

INTRODUCTION

Stigma is at the centre of the experiences that many service users encounter when in contact with their peers and with the communities they belong to[1-3]. The word stigma originates from ancient Greek and means 'a mark of shame or discredit'[4]; this defines the exclusion and marginalisation that many people with mental ill-health experience. Two elements to stigma have been defined: Public stigma and internalised stigma[1]. Public stigma involves the construction of stereotypes about excluded groups. This process leads to prejudice which is translated into active discrimination and marginalisation against this population[1]. Self-stigma[1,5] involves the internalisation and acceptance of negative beliefs about mental illness. These elements interact[5] because people who live with conditions such as schizophrenia may also endorse stereotypes about themselves, leading to "self-discriminating behavior" such as self-imposed isolation derived from the stereotype held by others about their "risky and dangerous" behaviours. Self-stigma reduces individuals' self-efficacy and self-esteem[1,5]; moreover, internalized stigma can disrupt mental health treatment-seeking intentions and behaviours and can lead to delayed help-seeking[6]. Stigmatisation processes can also affect family members of people diagnosed with mental ill-health.

This article will explore my lived experiences of stigma as a person with a diagnosis of mental-ill health and reflect on the response by peer groups to my condition. It asks questions about the nature of both public and internalised stigma[1,5] and investigates the lack of understanding of mental health symptoms. I explore the processes that can challenge both public and internalised stigma and suggest how anti-stigma campaigns can confront discrimination. I finally propose how acts of empowerment and the concept of recovery can both challenge stigma and promote greater understanding of mental ill-health.

METHOD OF REFLECTION

I am both a social work academic and service user expert with a diagnosis of schizophrenia. Both these identities are central to the construction of this article as I reflect and analyse my experiences about the nature of stigma. At the centre of social work is the process of reflection and reflexivity, a method used to enable professionals to understand and make sense of their experiences[7]. Reflexivity enables a person to explore his/her experiences and interpret them to gain greater understanding of the context to the situation around him/her[7]. A useful method that enables reflexivity is a process that explores the art of writing and reflection in investigating practice[8]. This approach connects the narratives of lived experiences told through personal reflections to the context of practice[8], exploring the links between local encounters and the wider circumstances. I thus relate my lived experiences of stigma and illuminate their significance for understanding the wider environment through a process of reflection. This method has been used in health, social care, and education and can facilitate an investigation of the significance of personal reflection in the setting of professional practice[8].

MY REFLECTIONS

This is for me a frightening and revealing reflection. It focuses on my sense of shame and stigma as a person with mental ill-health. It is hard to write as this process reveals details of experiences I have not spoken of before or allowed to bubble to the surface. These are accounts which I have hidden deep and buried in forgotten memories. They are embarrassing and shameful-and best forgotten. But at times they can't be forgotten and come to the surface.

At the time of the experiences described in this reflection, I was very paranoid and found it difficult to manage my mental health symptoms. I heard conversations and thought that people were talking about me. I translated the words I heard into what I wanted to hear – words that had been unsaid. These are my demons of lived experience through the shame and embarrassment I encounter as I remember them.

I experienced a mental health crisis involving extreme paranoia and psychosis at the age of 18-years-old. This happened at university in the North of England in the early 1990s. At the time I was studying at university far away from home. I had no personal experience of mental ill-health and had no inkling or understanding of its manifestation. At that time, I believed that mental illness happened to "mad" people, and was not something I would experience; moreover none of my peers or tutors recognised the signs of a pending mental health crisis until the illness was quite advanced.

My parents came to visit me at my university; this visit coincided with my first episode of mental health crisis. My mother stayed in the university as my mental health was deteriorating. I eventually had an appointment to see a psychiatrist and was admitted voluntarily for a short hospital stay and prescribed medication. On leaving hospital, I continued to take medication and returned to university. I continued to experience paranoia and low levels of psychosis and was eventually diagnosed with schizophrenia two years later. I continued my university studies, with great difficulty, and finally graduated. I was awarded a lower degree classification than previously predicted; however, completion of my university degree was a real achievement.

However, alongside this success at completing my degree, I also experienced many episodes that caused (and still cause) me shame and embarrassment. I remember back to experiences of when I was unwell, and I cringe. After leaving university I returned home to live with my parents. I was very lonely and isolated and craved a relationship with somebody who would like me for who I was, support me and take care of me. I was naïve, dependent, and overweight, because of the increased appetite associated with taking the prescribed anti-psychotic medication. I had little self-confidence and felt a sense of shame at who I was. I so much wanted to be valued.

There are so many memories that cause shame and embarrassment. I remember. I really liked somebody. This person was in a social club which I joined at the age of 23-years-old. The social group was a small group of 10 people for those aged 20-30-years-old (It wasn't a mental health peer group, but a social group in the community). There were some people who became my friends in the group; they were kind and thoughtful, but some who were unkind and found a mental health issue to be amusing. The group members all had more "success" than me. I was still living at home, undertaking additional study, and trying to forge a life for myself. But I was still dependent on my parents, and I lacked self-worth. This person who I liked didn't like me. I couldn't accept it and I believed that he liked me.

I listened like a snake to the conversations of other people. I listened to their conversations for evidence that he liked me. I heard things the people didn't say, and when I would go over their words, I would hear the words that he liked me. Words that hadn't been said, but I remembered as being said. Few people without lived experience of mental ill-health, can understand how paranoid beliefs may be perceived as a true representation of the world; my peers couldn't understand that I believed these thoughts to be true. At times people in this group teased me because I was a sad and very lonely person. They would say that he liked me, but he didn't; some people teased me because I couldn't seem to accept the obvious. During this period, I was like a ship, lost at sea, hurtling from one wave to another. I always ask the question: Did those people treat me unkindly and without compassion, or did they just not understand? As I remember I cringe with embarrassment and shame. Was it my fault? I had a mental health illness. They didn't understand the impact on me.

To my lasting shame and stigma, I had a pattern of such behaviour. I would latch onto somebody and believe he liked me. I was lonely and isolated and so wished for somebody to care for me. Previously to this experience, I kept such thoughts silent and did not share them, but this situation was different as I truly believed he liked me. I

was a persistent re-offender! My behaviour wasn't obvious, and I didn't harass him, I was a bit of a "silly nuisance"! He didn't understand my pain and embarrassment, I don't think he noticed me, only I experienced the shame.

This internalised failure is linked to the messages I reinforced to myself when I wasn't well. You can't do that. You aren't good enough to do that. You are no good. These are the demons of internalised stigma that say you can't achieve; that you are no good. This is a narrative of pain. I was bullied, undermined, and shamed as they laughed at me. Did they know the impact on me?

I managed the day-to-day stigma by convincing myself that I was of no value and self-reinforced the stigma others felt towards me; this meant my confidence plummeted. This was a negative coping mechanism which was effective because it dulled all hope and optimism; I couldn't be hurt anymore and couldn't fall any further because I had failed utterly.

What saved me from being this sad and lonely person? Eventually by engaging with learning, study, and being supported by mentors throughout my social work career, I began to achieve and to succeed. I studied for a Master of Arts degree in Social Work, then a PhD. Work for me was at the centre of my recovery journey and enabled me to fight the stigma; it led to a passion to change public stigma for those experiencing mental distress. Finding a wonderful and considerate and understanding man who became my husband was at the centre of my recovery. I am not now the person who was that person at that point in time described in my reflection. I cringe at my loneliness, my embarrassment, my shame, and my isolation. Was it my fault or was it part of my recovery journey?

DISCUSSION

The meaning of stigma and its impact on my life

In the following section I discuss my reflection and contextualise the experiences in the wider literature which seeks to explore the impact of mental health stigma in society. It is important to illuminate how stereotypes and prejudice impact on people with lived experience, and lead to their sense of shame and exclusion from society. Figure 1 highlights different types of stigma encountered in my life which resulted in my low self-esteem, poor self-efficacy and which limited my recovery. It provides a framework to explore discussion in this article. The elements of stigma represented in Figure 1 include: Public stigma, structural stigma, associative stigma, personal stigma, perceived stigma, and self-stigma. Alongside the cycle of stigma, my own experiences of double discrimination as both a woman and a person with lived experience of mental ill-health are depicted; these underpin the experiences of social bullying. Whilst parallel to these feelings, but outside of my direct encounters, the associative and affiliate stigma experienced by my family are identified. Finally factors that help to challenge stigma in society, such as protest, education, and contact push out against the cycle of stigma to counteract discrimination and marginalisation. These factors, captured in Figure 1, are elucidated in the article discussion.

The social identity of a person with mental ill-health is often negatively construed because the individual does not conform to social expectations of working and living independently[9]; this thus leads to them being stigmatised and devalued and experiencing public stigma. Furthermore, as people absorb this negatively constructed social identity, this then leads to forms of internalised stigma, or self-stigma, in the individual because of negative attitudes aimed at them.

The stigma encountered by people with mental health issues has been widely explored in research[1,2,5]; perhaps the most well-known forms of stigma are public and self-stigma[1]. However, stigma exists in many forms across cultures[2]: Within the individual (self-stigma), interpersonally (personal stigma), in the shared beliefs of a social group (public stigma), and in the policies and practices that structure society (structural stigma). Figure 1 shows the elements of stigma which constrained my recovery, first exemplified in structural stigma derived from public stigma.

Structural stigma is an important concept to highlight as it expresses how stigma can exist throughout a culture and become endemic in a system[9]. From my narrative, it seems clear that my peers believed that it was acceptable for them to tease me because I was a person with mental ill-health to be pitied and undermined. The acceptance of structural stigma[9] allowed them to bully me because I was a person who was devalued and of no worth.

Furthermore, three different reactions[10] by the community to people with mental health issues have been identified. Firstly, authoritarianism is the belief that people



Figure 1 Experiencing and challenging different forms of stigma.

with mental health issues are not able to take care of themselves and need other people to take control and direct their lives. Secondly, there is a response to people with mental ill-health that is based on fear and exclusion. This reaction is founded on the belief that people with mental health problems are dangerous and should be isolated from their communities. The final reaction generated in response to people with mental ill-health is benevolence. This response is based on the belief that people with mental health issues are innocent and naïve and not able to make decisions for themselves, resulting in paternalistic help being offered. Such a reaction from peers in their community is often compounded with feelings of annoyance and anger towards people with mental health issues.

Thus, in my experiences I was a person to be excluded and isolated; my peers also felt a benevolent response towards me. I was treated with paternalism as they directed annoyance and anger towards me. I was to be pitied but simultaneously an object unable to manage her own emotions, unable to live independently, of potential risk because I failed to respond in "normal" and socially acceptable ways to my peer group. The process of structural stigma led to a sense of low self-esteem and poor self-efficacy, as illustrated in Figure 1.

Furthermore, six further forms of public stigma have been highlighted[11]; however only three are mentioned here which I particularly relate to in the context of this article. I thought I was unable to fulfil social positions (exclusionary sentiments); I believed my mental health treatment had negative effects on my social status; (treatment carryover concerns) and I believed my family experienced negative consequences from my mental health status (disclosure spillover).

Associative and courtesy stigma[11,12] were encountered by my family members This type of stigma is a process in which a person is stigmatized by virtue of his/her association with another stigmatized individual. Additionally affiliate stigma occurs when care-givers' psychological responses to caring are impacted by the public stigma that prevails in society and they internalise self-stigma[13]. My parents supported me to the best of their ability, but they didn't always understand the shame and stigma that I experienced. My family felt personally impacted by the negativity of my diagnosis; and were unable to talk to their peers in their community, encountering affiliate stigma[13]. As shown in Figure 1, their experiences were encountered in parallel to my exclusion but were different to and outside of the stigma I suffered as a person with a diagnosis of schizophrenia. They sought support from peer and mutual aid support groups at moments in their caring journey. However, I felt uncomfortable with them attending such groups because I believed they talked solely about my mental ill-health in these environments. I didn't recognise or acknowledge that they had their own needs as care-givers. However, eventually, the fears I expressed prevented them from accessing any forms of support. My parents were therefore further isolated through

the feelings of self-stigma; and, thus, stigma limited the recovery of both me and my social network.

These elements suggest that underpinning public stigma[1] are elements of fear[14], a desire to keep a social distance[10], a devaluing of the role of people with mental health issues[9]; fears that association with someone with a mental health issue can cause feelings of exclusion[10] or "courtesy stigma" and associative stigma[11,12]. These elements connect to the process of self-stigma in both myself and my parents[1,11] associated with internalising the notions of social exclusion and the inability to manage an independent life[14]. These elements of exclusion led to the belief that I was deserving of pity, that I was shameful and thus deserving of stigma.

The issue of perceived stigma may also be in play in this context[15,16]. Perceived stigma concerns how a person with mental ill-health anticipates a negative reaction from others about their diagnosis; it is particularly relevant to those people who want to be open about their diagnosis[15]. Moreover, this interacts with a sense of self-stigma as indicated in Figure 1. I anticipate a negative reaction from some people in my social circles and thus choose not to disclose my diagnosis. For example, I have not shared my diagnosis with some close family members from a fear about how they might react-I perceive that the diagnosis of schizophrenia is often linked to notions of dangerousness and anticipate a negative response. However, although I choose not to reveal my diagnosis in many social settings, I often divulge these experiences in many academic circles[17]. I have a passion to use my expertise-by-experience to change mental health services for the better and yet feel a need to protect myself from people who don't understand mental ill-health. This decision about when to reveal my diagnosis leads to an anomaly of when I choose to disclose my status and when I choose not to[17].

Returning to my experiences of exclusion, women with mental health conditions[18] often experience social devaluation through a double disadvantage based on the intersection of being both a woman and a person with a mental health condition. Such discrimination was reflected in the historical devaluing of women through the early diagnosis of hysteria, labelled as a mental health condition linked to women's health and reproductive cycles[18]. Women with mental illness, who have experienced trauma, highlighted more difficulties with low self-esteem and the stigma connected to lived experiences than women who have not experienced trauma[18]. The trauma and social bullying that I received ripped out my sense of self-esteem and self-efficacy, limiting my recovery and leaving me a pitiable and empty shell. This process of stigma is depicted in Figure 1, whilst the double discrimination of being a woman and having lived experience of mental ill-health is illustrated as existing alongside these feelings.

Furthermore, the connection between perceived stigma and experiences of victimisation for people with mental health needs has been considered in other studies[19]. Perceived stigma and victimization are significantly associated, and the stigma attached to mental illness[19], from being perceived as being dangerous, violent, or undesirable, is a statistically significant predictor of victimization experiences. However, there is little understanding of the experiences of those with mental health issues; particularly as women with mental ill-health often experience an intersection of stigma and victimisation by their peer and friendship groups[18,19], as I describe above.

More widely, the cultural heritage of people with mental ill-health can impact negatively on their experiences of acceptance in their peer and friendship groups[10,20]. Public from Eastern countries ascribed more moral attributions to people with mental illness than from Western cultures[10], thus increasing the potential to discriminate. Moreover, people from Western countries endorsed higher stigma (prejudice and discriminatory potential) and made more moral attributions when the target was a minority (as compared with majority) group member. Furthermore, concern for loss of face in Eastern cultures is part of the process preventing individuals from seeking help from mental health providers to prevent shaming one's family[20], because mental health conditions are highly stigmatized in Chinese communities. In the United Kingdom, there has been an ongoing national anti-stigma campaign, Time to change, which has sought to challenge stigmatisation and discrimination against people who experience mental ill-health[21]; it has achieved some limited success.

This section has underlined the stigma and discrimination experienced by people with mental ill-health, highlighting the potential of victimisation to this group, and particularly to women who experience double discrimination. Figure 1 captures how I have experienced different types of stigma which have limited and bounded my potential recovery journey, and that of my family. Subsequently, an acknowledgement of the importance of cultural heritage in this context has also been considered. In the next section the paper considers how society can challenge the stigma and marginalisation of those who experience mental ill-health.

HOW CAN SOCIETY CHALLENGE STIGMA?

People with mental ill health may sometimes challenge this sense of self-stigma through reactions of "righteous anger"[1] about the negative social identity ascribed to them by their community. Moreover, a sense of righteous indignation, particularly associated with collective activism and group identity, can challenge both individual and group prejudice. For example, the experiences of 800 gay and bi-sexual men were explored[22] and a sense of belonging and group activism was positively associated with improved self-esteem; indeed, extrapolating to mental health there may be "high feelings of self-esteem" from "experiencing group identity"[1]. Despite this process of empowerment, individuals who are stigmatised can resist this label by claiming their own exceptionalism to the stereotypes, thus challenging stigma as an individual[2].

A process of empowerment can help people to gain a sense of control in their lives and can foster independence and agency[5], challenging the stigma they may experience that results in dependency and low self-efficacy. Indeed, "empowerment is the flip side of stigma, involving power, control, activism, righteous indignation, and optimism"[5]. The importance of empowerment in tackling self-stigma is reinforced in the context of promoting control over treatment choices and the direction of one's life[23]. Empowering people in these choices can increase a sense of autonomy and agency, thus resulting in a positive effect on self-stigma.

Empowerment cannot happen without change in individuals and the systems around them. From their standpoint as art therapists[24], the issues of stigma and shame met by people with mental health issues were surveyed in one study. This study noted how people with mental ill-health are often devalued in society and their role is seen as inconsequential. Such ideas in the field of mental health are related to the context of learning disability, where the importance of social role valorisation is explored, a concept[25] developed to understand the need to empower people with learning difficulties and enable them to be respected and valued in their social role.

In the discussion above, it was identified that stigma against people with mental health needs derives from having a negatively construed social identity. The field of learning disabilities research offers a lot to learn in supporting the promotion of people with mental health issues as full and respected citizens with a valued social role. This leads to the question of how can society combat both public and self-stigma?

EFFECTIVE METHODS TO PROMOTE ANTI-STIGMA WORK

Three strategies to help overcome mental health stigma are explored in the literature[10] : Protest, education, and contact. Firstly, protest is the process of challenging people's negative beliefs through direct action. Secondly, education involves the provision of brief courses or facts to counteract prejudice. Finally, contact consists of directly promoting one-on-one contact between people with lived experience of mental ill-health and the public. Contact is found to be the most effective way of challenging stigma and changing attitudes. Moreover, "face-to-face contact with the person, and not a story mediated by videotape, had the greatest effect" at challenging stigma[21]. The role of each of these factors in challenging stigma is illustrated in Figure 1, as they push out of the cycle of stigma that I depict as representing my experiences.

Anti-stigma campaigns need to balance wide and broad approaches that seek to challenge discrimination in a large population of people with more local campaigns which focus on challenging the opinions of small groups[26]. This finding is reinforced by another study[27] which suggests that such strategies could be developed to also reduce self-stigma in people experiencing mental health issues. However, little is known about what elements of contact are effective in challenging stigma[10]; for example, is it equal status or promoting understanding about experiences of mental ill-health that makes contact-based strategies effective? It is essential to answer this to understand how to effectively tackle discrimination and marginalisation of people with mental ill-health.

Encouraging people with mental health needs to disclose their mental health condition may help to reduce stigmatization as individuals take control of information about their health condition and can become empowered[5]. However, on one hand, disclosing psychiatric status can have negative implications because it can cause discrimination and prejudice, on the other, people who disclose often report lower levels of self-stigma, a greater sense of personal empowerment, higher self-esteem, and enhanced quality of life[5]. Despite this, the value of disclosing a diagnosis such as schizophrenia is questioned because of the high stigma associated with this

condition[28].

It appears that the process of "contact" to reduce stigma needs to be carefully managed. There needs to be further research about what elements of contact effectively challenge stigma[10] and how people with a mental health condition can be appropriately supported through the process of disclosure[28]. Empowerment is key to challenging self-stigma and enabling the person to challenge both self-stigma and public stigma. Moreover, difference and disdain are key measures of stigma; a recent study explored how to manage these issues in the context of mental health[29]. They investigated how difference results in people with mental illness being alienated and othered making a separation of "us" from "them". Consequently, this sense of difference leads to disdain because people with mental illness are devalued and disrespected. The study concludes that anti-stigma efforts may best be focused on tackling elements of disdain, rather than difference, because disdain seems to be the main driver of self-stigma[29]. This focus on empowerment can be achieved by promoting messages such as: "I may be different, but I am not a person of lesser value."

Moreover, in the United Kingdom, the anti-stigma campaign, Time to change[21] has achieved some success in challenging stigma through publishing the personal narratives and stories of those who have lived experience of mental distress; this reflects the acceptance by service users that they may be potentially "different" from other people in society and may have different stories to tell, but that they are not of lesser value. Maybe other people without lived experience of mental distress come to acknowledge their own differences and idiosyncrasies as art of the process of learning about differences?

CONCLUSION

Empowerment through recovery

Such processes of empowerment build on the seminal work in the field of learning disability theory of social role valorisation[25] that highlights the importance of having a respected and valued role in society. Furthermore, empowerment, enhancing service user control, and self-management of a mental health condition are at the centre of the recovery approach[30] an aspirational practice in mental health that emphasises the importance of people with mental ill-health leading a good life despite the limitations of their illness[31]. Indeed, recovery is, in itself, an "effective message" to combat stigma because it reinforces that "mental illness does not keep a person from achieving a full range of positive outcomes"[30]. This process of empowerment through promoting recovery may be a key factor in challenging both the public stigma and self-stigma of people who have mental ill-health because recovery emphasises the importance of achievement, respect and value for this group[31].

As my reflection shows, occupying a valued social role and beginning to follow my dreams enabled me to begin to reconstruct my brittle self-esteem and self-efficacy. Little by little, building on confidence and true friendship, I was enabled to take on a responsible role as an academic and increase my capacity to perform[32,33]. Recovery was at the centre of my empowerment and led me to a place of increased confidence and self-esteem[32,33] where I was able to combat my own sense of self-stigma and challenge the public stigma of being a person with a diagnosis of schizophrenia. This place led me to exorcise the demons of lived experience. Thus, drawing on the research presented in this article, it is suggested that increased contact between people with lived experiences, and their peers in the community, based on respect and value[10,28], and the representation of stories of recovery[32,33], may be at the centre of promoting the social value of people with mental ill-health.

ACKNOWLEDGEMENTS

Thanks to Linda Homan for reading and reviewing my article.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 March 19; 11(3): 73-86

DOI: 10.5498/wjp.v11.i3.73

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

Using eye movements in the dot-probe paradigm to investigate attention bias in illness anxiety disorder

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Author contributions: Zhang YB and Wang PC contributed equally to the study, both collected data, conducted statistical analysis, and drafted the manuscript and are parallel first authors; Ma Y, Yang XY, and Meng FQ collected the data; Broadley SA edited and commented on the manuscript's intellectual content; Sun J and Li ZJ both contributed to the study equally; Sun J conducted statistical analysis, critically reviewed, edited, and revised the manuscript; Li ZJ designed and supervised the study.

Supported by the Capital Health Development Research Project, No. 2016-1-2121.

Institutional review board statement: The study was approved by the Ethics Committee of Beijing An'Ding Hospital, Capital Medical University.

Informed consent statement: All

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Abstract

BACKGROUND

Illness anxiety disorder (IAD) is a common, distressing, and debilitating condition with the key feature being a persistent conviction of the possibility of having one or more serious or progressive physical disorders. Because eye movements are guided by visual-spatial attention, eye-tracking technology is a comparatively direct, continuous measure of attention direction and speed when stimuli are oriented. Researchers have tried to identify selective visual attention biases by tracking eye movements within dot-probe paradigms because dot-probe paradigm can distinguish these attentional biases more clearly.

AIM

To examine the association between IAD and biased processing of illness-related information.

METHODS

A case-control study design was used to record eye movements of individuals

patients gave informed consent.

Conflict-of-interest statement: All authors declare that they have no conflict of interests.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at ksiaaleila@yahoo.fr.

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Manuscript source: Unsolicited manuscript

Specialty type: Psychiatry

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 1, 2020
Peer-review started: December 1, 2020
First decision: December 12, 2020
Revised: December 23, 2020
Accepted: January 28, 2021
Article in press: January 28, 2021
Published online: March 19, 2021

P-Reviewer: Llanes-Jurado J
S-Editor: Zhang L
L-Editor: Filipodia
P-Editor: Li JH

with IAD and healthy controls while participants viewed a set of pictures from four categories (illness-related, socially threatening, positive, and neutral images). Biases in initial orienting were assessed from the location of the initial shift in gaze, and biases in the maintenance of attention were assessed from the duration of gaze that was initially fixated on the picture per image category.

RESULTS

The eye movement of the participants in the IAD group was characterized by an avoidance bias in initial orienting to illness-related pictures. There was no evidence of individuals with IAD spending significantly more time viewing illness-related images compared with other images. Patients with IAD had an attention bias at the early stage and overall attentional avoidance. In addition, this study found that patients with significant anxiety symptoms showed attention bias in the late stages of attention processing.

CONCLUSION

Illness-related information processing biases appear to be a robust feature of IAD and may have an important role in explaining the etiology and maintenance of the disorder.

Key Words: Attention bias; Selective attention; Eye tracking; Dot-probe; Illness anxiety disorder; Disengagement

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Core Tip: This is the first study which has examined patients with illness anxiety disorder (IAD) having an attention bias that is mainly manifested as attentional avoidance at the early stage and overall attentional maintenance when presented with illness-related stimuli. They also have demonstrated vigilance of attention at the early attention stage and overall attentional maintenance when presented with disease and positive/neutral stimuli. In addition, this study found that patients with suspected disorders with significant anxiety symptoms show attention bias in the late stage of attention processing and struggle to dismiss the stimulus, showing delayed detachment. This study suggests that patients with IAD have attention bias and this may have provided a new way of identification of IAD symptoms using an eye-tracking evaluation method.

Citation: Zhang YB, Wang PC, Ma Y, Yang XY, Meng FQ, Broadley SA, Sun J, Li ZJ. Using eye movements in the dot-probe paradigm to investigate attention bias in illness anxiety disorder. *World J Psychiatr* 2021; 11(3): 73-86
URL: https://www.wjgnet.com/2220-3206/full/v11/i3/73.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i3.73

INTRODUCTION

Illness anxiety disorder (IAD) is a common, distressing, and debilitating condition, with the key feature being a persistent conviction of the possibility of having one or more serious or progressive physical disorders[1]. IAD was formerly named hypochondriasis in DSM-4. Currently, the reported prevalence is approximately 1%[2-5]. Patients manifest persistent somatic complaints or a persistent preoccupation with their physical appearance. They repeatedly seek assurance from medical advice for physical symptoms that they think they have, and frequently have doubt or fear about negative medical test results and doctors' explanations[6]. This type of preoccupational thought persists despite appropriate medical evaluation and medical reassurance. The course of IAD is usually chronic and fluctuating, associated with costly and unnecessary medical reexaminations and the overuse of medical resources[5].

According to cognitive-behavioral models of IAD[1], IAD patients seem to hold faulty health beliefs. The dysfunctional assumptions about their bodily symptoms and

illness may be triggered by critical incidents. It has been argued that the dysfunctional beliefs about illness and misinterpretation of bodily symptoms appear to be specific and important for patients with IAD and to be a highly specific characteristic of IAD[7,8]. They tend to show a more restrictive concept of good health than do anxiety patients and healthy people[8]. They are hypervigilant to bodily symptoms or tend to amplify benign physical sensations[9-11].

It has been proposed that these psychological processes may underpin the symptoms of IAD. A cognitive-behavior therapy (CBT) for IAD that is derived from W and S's model has been effective. CBT patients had lower levels of health-related anxiety and less impairment of social roles, but IAD somatic symptoms were not improved significantly by CBT[11,12]. Other researchers have observed a positive correlation between the feature-positive effect (FPE) and illness anxiety concerns[13]. The FPE is the bias of overweighing positive and underweighing negative information. The FPE may explain the interesting fact of the IAD's sensitivity to illness cues and insensitivity to medical reassurance or negative medical results, but it cannot fully explain the initial preoccupation with bodily complaints and health.

IAD is characterized by patients focusing their attention on one or two organs or systems of their body. They attend to information that confirms their worry and conviction, but simultaneously ignore and under-weigh negative results of medical investigations and evidence of good health. Thus, they display a type of information processing bias, and cognitive processes are considered relevant to the etiology and maintenance of IAD[14].

Attention bias refers to the individuals who have different attention distribution to the corresponding threat or related stimulus, relative to the neutral stimulus[15]. Researchers studying attention bias found patients with mental illness often allocate their attention towards concern-related or mood-congruent material. A key feature of attention biases is anxiety increasing patients' attention to danger and threat-related stimuli[16]. Patients have attention bias in favor of stimuli referring to their specific disorder, and interpretational bias leads them to allocate their attention to these stimuli as more relevant. Thus, their bias is specific to the meaning of stimuli relevant to the disorder. In people with anxiety disorders, anxiety stimuli are likely to receive attention bias when they are danger or from threat-related stimuli, but in people with IAD, the content and disorder specificity of the stimuli is unclear. More recently, some non-illness-related attentional stimuli have been suggested to maintain IAD concerns; in other words, the attention bias may not be limited to illness-related stimuli but also include non-illness-related stimuli[17,18]. In sum, empirical evidence regarding measuring attention bias in IAD is scarce and equivocal.

To date, a prominent means to evaluate visual attention is the emotional stroop task. Researchers have regarded increased color-naming latencies of emotional or concern-related words as an indicator of selective attention bias, but unfortunately the emotional stroop task cannot differentiate the two possible mechanisms a facilitated engagement or a delayed disengagement[19,20]. So the precise course of such biases is obscured by the mixed nature of the test process. Alternative experimental paradigms regarding attention bias, such as the dot-probe investigation and the Posner cued-target paradigm, can distinguish these two possible biases more clearly[21,22]. Because eye movements (EMs) are guided by visual-spatial attention, eye-tracking technology is a comparatively direct, continuous measure of attention direction and speed when stimuli are oriented. 'Persistent', the dot-probe experiment, which uses EM tracking, has been undertaken primarily to examine attentional processing among anxiety disorders and in pain-related research. Researchers have tried to identify selective visual attention biases by tracking EMs within dot-probe paradigms with success[23,24]. These studies investigated individuals with high social anxiety, generalized anxiety disorder, and depressive disorder, using EMs and a modified probe detection task to pictures of faces. They found that anxiety individuals initially directed their gaze toward neutral faces more often, but were quicker to look at emotional faces and looked at emotional faces for less time. Therefore, anxiety individuals were consistent with a vigilant avoidant pattern of bias, compared with other people.

Using the dot-probe paradigm, our primary aim in the current study was to explore the specificity of attention bias in IAD. We hypothesized that patients with IAD, compared with healthy controls, show more attention bias for illness-related information when negative pictures, positive pictures, and neutral pictures are presented simultaneously. In addition, we hypothesized that patients display orienting attention biases, reflected by fixating first and more rapidly on illness stimuli than other alternatives. We analyzed differences in EM indices reflecting subsequent bias in attention maintenance, including duration of first fixation, average fixation and total gaze/first fixation, and overall gaze duration.

MATERIALS AND METHODS

Study design and participants

A case-control study design was used for the study, with the sample consisting of an IAD patient group and a healthy control (HC) group. Participants were recruited *via* e-mail and newspaper advertisement from Beijing An'Ding Hospital. The patient group fulfilled the criteria for IAD (DSM-5 and formerly named hypochondriasis in DSM-4) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[25]. Patients were screened with the Structured Clinical Interview for DSM-IV-TR Axis I Disorder (SCID-I) and Structured Clinical Interview For DSM-IV-TR Axis II Disorder (SCID-II)[26] to affirm the initial axis I disorder diagnosis and axis II personality disorders. Interviews were led by independent, professionally trained clinical psychologists. The HC group was matched to the patient group in age, sex, ethnicity, and education. People who were unable to use their hands, or those with a serious head injury or psychiatric illness, were excluded from the study. All participants had normal or correct-to-normal vision and color vision and no neurological disease, psychiatric illness, or medication use for any psychiatric disorder. Their age ranged from 18 to 60 years, and their education level was 9 years or more.

Ethical approval for this research was obtained from the Beijing An'Ding Hospital, Capital Medical University Research Ethics Committee [Ethics number: (2014) Research (No. 38), Funding number: 20131107110012]. All participants were fully informed about the study research and provided with a general overview of the dot-probe task. All participants provided written informed consent before they agreed to participate in the research in compliance with the regulations of the institution and the guidelines of the Declaration of Helsinki. They were free to terminate the experiment at any time they wished.

Materials

The stimuli used in the dot-probe task consisted of 128 pictures; we collected these pictures through Baidu image search, a search engine in China, which were grouped into four main categories: Illness-related, social threat, positive, and neutral pictures. Illness-related pictures included pictures about patients in disease/hospitals/doctors/doctors threating or checking patients and pictures about oral medicine. Social threat pictures included pictures about earthquake/quarrel/flood/wars/fires/explosion/traffic/fighting/bridge collapse/plane crash/chasing by animals. Positive pictures included mountain/flowers/children/bird/women/wedding/congratulation/dancing. Neutral pictures included pictures about furniture/meeting/beautiful scenery/shopping/roads/clothes. These pictures have clear meaning, clear content, and try to highlight the stimulus itself; at the same time, these pictures cover as wide range of meanings as possible. The color of the images was unified with Photoshop CS 6.0 about brightness, saturation and contrast. Illness-related and social threat pictures were included to determine whether IAD patients were associated with a specific threat-related attention bias or any threatening material. Positive pictures were included to examine whether a general emotional response accounted for any effects found. These images were randomly presented to participants for 2 s each. Each picture size had mean height of 4.6 cm and mean width of 6.5 cm.

Sixty healthy volunteers were recruited to classify the pictures into our four predefined categories in our pilot study. These volunteers had normal or correct-to-normal vision and color vision. They were not on any medication and had no diagnosed medical or mental health condition. Among 400 pictures, 272 (68%) pictures were excluded as they were not allocated to the correct picture category by at least 80% of the raters. The final number of selected pictures for trials was 128.

Apparatus

Stimulus pairs were presented on a DELL 19 inch TN screen, with 1980 × 1024 pixel resolution and a 60 Hz refresh rate.

EM data were recorded *via* an sr research eyelink 1000 device (sr research, Canada; https://www.sr-research.com/). The experiment was programmed and run with sr research experiment builder. The eye-tracker sampling rate was 1000 Hz, with a spatial accuracy greater than 0.5° and a resolution of 0.01° in the pupil-tracking mode. An infrared motion system tracked em/head motion. A forehead and chin rest kept viewing distance constant and minimized head movements. Participants sat 60 cm from the monitor screen, resulting in a 29 cm horizontal, 22 cm vertical visual field.

Prior to the task, a standardized 5-point calibration procedure was performed.

EM data were recorded during each trial, starting shortly before and terminating immediately after picture-pair presentation (Figure 1).

Selective attention task

Selective attention bias was assessed in a visual dot-probe paradigm. With traditional dot-probe tasks, stimulus pairs are presented in separate spatial locations (*e.g.*, left *vs* right side of computer screen) and replaced by a probe in the location previously occupied by one stimulus. For this study, the main focus was on EMs during stimulus presentation of different image types. Before the formal study, a brief training (four trials) was undertaken to increase familiarity with task requirements; training procedures were identical to those used in the formal study with the exception that different pictures were used for the present study. Participants were told that in each trial of the forthcoming spatial perception task, a triangle would appear in the right or left of the computer screen for 500 milliseconds (ms), followed by picture pairs to which they should carefully attend. Each trial of the task began with a central fixation cross (+) shown for 500 ms and then replaced by an image pair that appeared for 2000 ms. After 500 ms, the next trial began. The formal task included 224 pairs of cards presented in four blocks with 56 trials per block. The four blocks consisted of combinations of the four categories of picture meanings, including (1) Disease–neutral (*e.g.*, oral surgery *vs* rail), as shown in Figure 2; (2) Disease–positive (*e.g.*, infusion *vs* scenery), as shown in Figure 2; and (3) Disease–threat (*e.g.*, operating room *vs* traffic), as shown in Figure 2. Besides, there were four categories included as filling items in order to reduce the monotony of the test materials, including disease-disease, threat-threat, neutral-neutral, and positive-positive. Each pair of images was defined as a trial and each pair of pictures was presented randomly among the four blocks. Participants were given a 2-min break after the presentations of 56 pairs of pictures. On average, the task took 40 min to complete.

Procedure

After providing informed consent, participants were escorted to the eye-tracking experimental area. They were seated in a height-adjustable chair with their chin in a vertically adjusted chin rest. The chin rest was used to reduce participant head movements, ensuring that participants' eyes were level with the middle of the monitor on which the stimuli were presented, and to maintain participant eye distance from the monitor at 60 cm. They were instructed to free view the images at all times during each trial. Further, participants were asked to look at the fixation point before each trial to standardize the starting location of their gaze. On completion of the dot-probe task, participants were asked to fill in several questionnaires, including their self-reported measures of demographics. In addition, the Beck Anxiety Inventory (BAI)[27], Beck Depression Inventory[28], Illness Attitudes Scale[29], and Whiteley Index[30] were used to assess participants' clinical symptoms.

Statistical analyses

EM data was recorded using the Eyelink1000 tracking system (Canadian sr-research) and was processed by data retrieval. First, the trials affected by invalid calibrations and uncollected EM data were removed; as each pair had two stimulus-related trials, there are total 448 trials per participant, the average invalid trials in 30 IAD participants were 13.767 (3.07%), and the average invalid trials in HC participants were 13.500 (3.01%). Then, we used data viewer software to divide the positions of the two pictures in the same picture matrix into two interest areas and selected valid EM data, including the corresponding position of the first viewpoint, the first-fixation duration, the overall gaze durations, and the overall fixation frequencies in different interest areas. Then, they were exported to Excel (Microsoft) in text format and were collated and converted in Excel to obtain the following attention bias scores: The first-fixation direction bias score = number of views (the first view of a certain type of stimulus) / effective trials; First-fixation duration bias score: The average viewing time (the first view of a certain type of stimulus); Overall gaze duration bias score = total time gazing at a certain type of stimulus/total time gazing at all stimuli in the trial; Overall fixation frequency bias score = the total number of times (viewing a certain type of stimulus)/the total number of times of viewing all stimuli in the trial. The general demographic data and scores of each clinical scale were measured using the international business machines statistical package for the social sciences studies V21.0 software package. Metrological data were represented by mean ± SD. All four EM indicators were statistically analyzed using independent sample *t*-test. The differences



Figure 1 Experimental setup for capturing eye-movement data.

between IAD group and HC group were compared on different types of images. The mean value of the group was compared with that of independent samples test, and $P < 0.05$ indicated that the difference was statistically significant.

Our study mainly examined four types of EM indicators: (1) First-fixation direction bias (%): The percentage of the number of first percentile points that an individual directs to the area of interest in which a certain stimulus is located as a percentage of the total number of active trials. It mainly examines the individual's initial attentional alert feature; (2) First-fixation duration bias (ms): In the disease–neutral, disease–threat and disease–positive image pairing, the difference reflects the early attention to the stimulation information in the area of interest; (3) Overall gaze duration bias (ms): During the entire experimental process, the total focus time of an individual on the area of interest of a certain type of stimulus accounts for the percentage of the total time spent staring at two pictures in the trial; and (4) Overall fixation frequency bias (%): Throughout the experiment, the total number of times an individual looks at the area of interest of a certain type of stimulus as a percentage of the total number of times a person looks at two pictures in the trial.

RESULTS

Table 1 depicts demographic characteristics and clinical symptoms of the IAD patient group and HC group.

Table 2 reports attention bias-related EM data, including first-fixation direction bias (%), first-fixation duration bias (ms), overall gaze duration bias (ms), and overall fixation frequency bias (%) in the IAD group and HC group (Figure 3).

First-fixation direction difference

When the participants were presented with the disease–neutral image pairs independent sample *t*-test showed there were significant differences in the first-fixation direction when presented with disease-related and neutral images in the HC group. When presented with disease-related images, the first-fixation direction of the IAD group was lower than that of the HC group ($t = -2.467$, $P = 0.017$); while presented with neutral images, it was higher than that of HC group ($t = 2.467$, $P = 0.017$).

First-fixation duration difference

When the participants were presented with the disease–neutral image pairs, independent sample *t*-test found that the first-fixation duration of the IAD group (280.476 ± 55.154) for the disease picture was significantly greater than that of the HC group (252.807 ± 45.075) ($t = 2.128$, $P = 0.038$). There was no difference in the neutral picture (IAD group: 288.280 ± 59.083, HC group: 264.668 ± 47.270; $t = 1.709$, $P = 0.093$).

When the participants were presented with the disease–social threat image pairs, independent sample *t*-test found that the first-fixation duration of the IAD group (281.20 ± 61.472) for the disease picture was significantly greater than that of the HC group (246.40 ± 30.991) ($t = 2.769$, $P = 0.008$). There was also difference in the social threat picture (IAD group: 296.86 ± 58.129, HC group: 266.37 ± 40.172; $t = 2.363$, $P =$

Table 1 Demographic characteristics and clinical symptoms of the illness anxiety disorder and healthy control groups

Item	Patient group: IAD group, *n* = 30	Control group: HC group, *n* = 30	t/χ^2	*P* value
Age in yr	30.03 ± 8.73	30.70 ± 8.61	−0.298	0.767
Sex, male/female	19/11	14/16	1.684	0.194
Educational background				
Junior high school	5	5		
Senior vocational/high school	4	4		
Junior college/university	20	20		
Master's degree or higher education	1	1		
IAS	47.53 ± 16.44	27.43 ± 13.07	5.240[c]	< 0.001
WI	7.60 ± 3.83	3.13 ± 1.98	5.677[c]	< 0.001
BAI	38.17 ± 12.09	24.57 ± 4.33	5.799[c]	< 0.001
BDI	18.10 ± 9.65	6.13 ± 6.71	5.577[c]	< 0.001

[c]*P* < 0.001.

BAI: Beck anxiety inventory; BDI: Beck depression inventory; HC: Healthy control; IAD: Illness anxiety disorder; IAS: Illness attitudes scale; WI: Whiteley index.

0.022).

When the participants were presented with disease-positive image pairs, independent sample *t*-test showed there were no significant differences in the first-fixation duration bias when presented with disease-related and positive-related images between the IAD group and HC group.

Overall gaze duration difference

When the participants were presented with the disease–social threat, disease-positive, and disease-neutral pairs, independent sample *t*-test showed there were no significant differences between the IAD group and HC group.

Overall fixation frequency difference

When the participants were presented with the disease–positive image pairs, independent sample *t*-test results showed the overall fixation frequency of the two groups toward the illness-related and positive images were different. Independent sample *t*-test showed the overall fixation frequency bias toward the disease images in the IAD group was higher than in the HC group (t = 1.841, P = 0.071), and fixation frequency bias toward the positive images was lower than in the HC group (t = -1.841, P = 0.071).

Attention bias-related EM and clinical symptoms

Regression analysis was used to investigate the correlations between the characteristics of the clinical symptoms of the IAD group and their EMs with various image pairs. The results showed that when the participants were presented with the disease–threat image pairs, their overall gaze duration bias toward illness-related images and BAI were found to have a positive correlation with disease-related images (β = +0.156, P = 0.045) and negative correlation with threat-related images (β = -0.156, P = 0.045) (Table 3 and Figure 4).

DISCUSSION

With the changes of diagnostic criteria, discussion about IAD is increasing these years. This study discovered that in the early and late stages of attention, the IAD and HC groups were different in their information processing for illness-related images and had corresponding attention mechanisms at different stages of attention.

In the early stage of attention, when presented with different pairs of socially threatening, positive, illness-related, and neutral images, participants in the IAD group did not manifest an attention bias toward illness-related images, and no vigilance

Table 2 Attentional bias-related eye-movement data

Item	Image classification	IAD group, *n* = 30	HC group, *n* = 30	*t*	*P* value
First-fixation direction bias as %					
Disease–threat	Disease	49.90 ± 9.93	49.94 ± 8.96	0.341	0.734
	Threat	50.10 ± 9.93	50.94 ± 8.96	-0.341	0.734
Disease–positive	Disease	34.90 ± 12.23	32.92 ± 9.77	0.693	0.491
	Positive	65.10 ± 12.23	67.08 ± 9.77	-0.693	0.491
Disease–neutral	Disease	45.00 ± 7.81	50.21 ± 8.53	-2.467[a]	0.017
	Neutral	55.00 ± 7.81	49.79 ± 8.53	2.467[a]	0.017
First-fixation duration bias in ms					
Disease–threat	Disease	281.20 ± 61.47	246.40 ± 30.99	2.769[b]	0.008
	Threat	296.86 ± 58.13	266.37 ± 40.17	2.363[a]	0.022
Disease–positive	Disease	272.16 ± 61.83	246.20 ± 35.4	1.996	0.051
	Positive	259.41 ± 49.95	238.71 ± 48.83	1.623	0.110
Disease–neutral	Disease	280.48 ± 55.15	252.81 ± 45.07	2.128[a]	0.038
	Neutral	288.28 ± 59.08	264.67 ± 47.27	1.709	0.093
Overall gaze duration bias in ms					
Disease–threat	Disease	44.90 ± 4.13	44.51 ± 3.86	0.388	0.700
	Threat	55.09 ± 4.13	55.49 ± 3.85	-0.388	0.700
Disease–positive	Disease	46.45 ± 5.3	44.35 ± 6.21	1.407	0.165
	Positive	53.55 ± 5.3	55.65 ± 6.21	-1.407	0.165
Disease–neutral	Disease	47.18 ± 4.13	46.97 ± 4.50	0.185	0.854
	Neutral	52.82 ± 4.12	53.03 ± 4.50	-0.185	0.854
Overall fixation frequency bias as %					
Disease–threat	Disease	45.63 ± 3.24	45.59 ± 3.83	0.051	0.960
	Threat	54.37 ± 3.24	54.41 ± 3.83	-0.051	0.960
Disease–positive	Disease	46.93 ± 4.43	44.67 ± 5.06	1.841	0.071
	Positive	53.07 ± 4.43	55.33 ± 5.06	-1.841	0.071
Disease–neutral	Disease	48.44 ± 3.78	48.76 ± 3.50	-0.341	0.735
	Neutral	51.56 ± 3.78	51.24 ± 3.50	0.341	0.735

[a]$P < 0.05$.
[b]$P < 0.01$.
HC: Healthy control; IAD: Illness anxiety disorder.

attention bias was observed. However, the first-fixation direction of IAD participants on illness-related images was shorter than that of the HC group, indicating that patients with IAD had an early-stage attentional avoidance bias on illness-related stimuli. Once the early visual attention of these patients was captured by symptom-related or socially threatening stimuli, they were less likely to disengage their attention to such stimuli, thus exhibiting delayed engagement bias. At the late stage of attention, participants with IAD presented a noticeable avoidance of illness-related images, which was manifested as a less overall fixation frequency on such pictures and more fixation frequency on positive, neutral and threat-related images. Therefore, the attentional pattern of patients with IAD was shown as an attentional delayed disengagement bias toward illness-related and socially threatening images, and an overall attentional avoidance bias to illness-related images.

The hypervigilance–avoidance hypothesis suggests that individuals tend to show instant vigilance, followed by swift avoidance, when presented with threatening

Table 3 Regression analysis of overall gaze duration bias (ms) and beck anxiety inventory

	Adjusted *R*-square	Regression coefficient (95%CI)	*P* value
Disease image	0.055	0.156 (0.004 to 0.308)	0.045
Threat image	0.055	-0.156 (-0.308 to -0.004)	0.045

CI: Confidence interval.

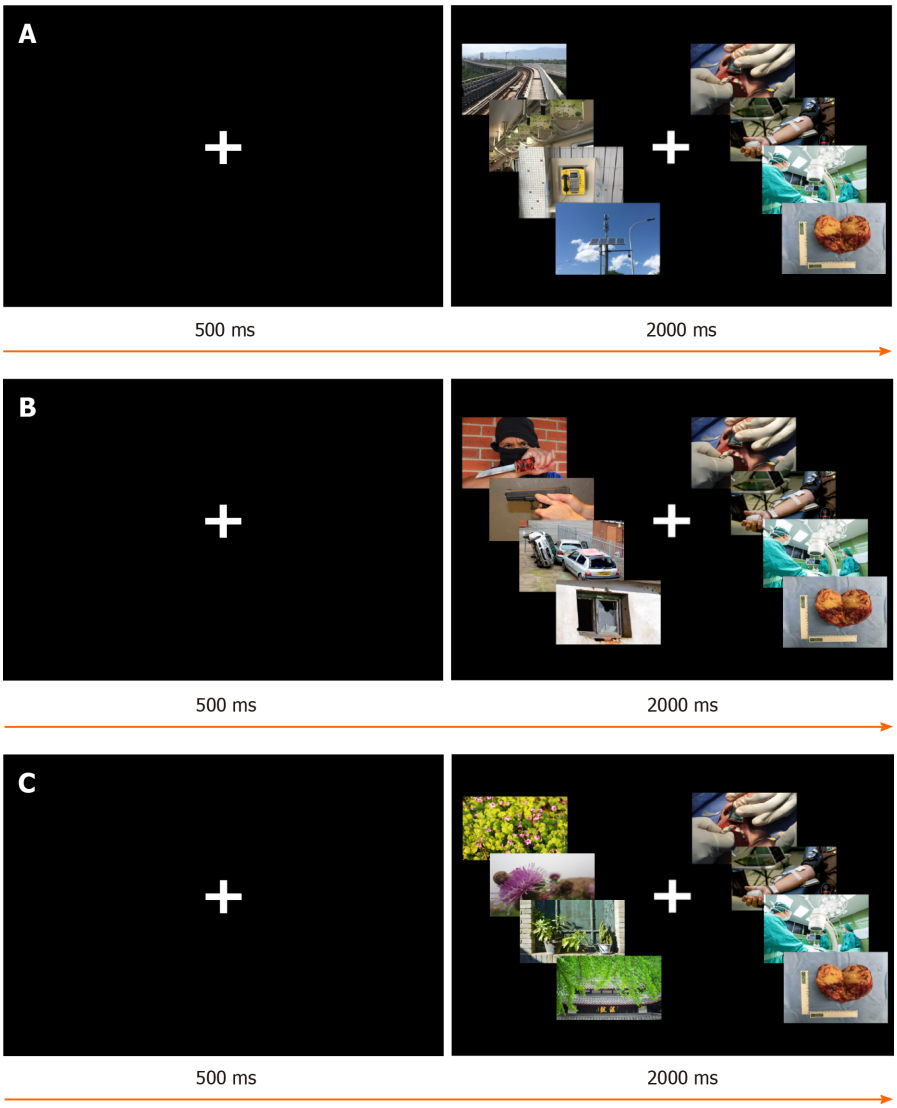


Figure 2 Disease–neutral picture, disease–positive picture, and disease–threat picture presentation examples. A: Disease–neutral (*e.g.*, oral surgery *vs* rail); B: Disease–positive (*e.g.*, infusion *vs* scenery); and C: Disease–threat (*e.g.*, operating room *vs* traffic).

stimuli to prevent further processing of threatening information. This attention mechanism allows individuals to detect more potentially threatening information during the early stage of attention. The attentional avoidance mechanism then hinders such information from being objectively evaluated, leading to a cognitive bias toward the threatening stimuli and creating a selective attention, judgment, and storage effect. For this reason, this study speculated that individuals with IAD have normal attentional processing mechanisms for stimuli related to neutral, positive and threat emotions. However, their longer attention engagement toward illness and threat-related information in the early attention stage and their overall avoidance mechanism in the late stage of attention may explain why they suffer from long-term processing failure of disease-related stimuli, and hence have psychological disorders.

Current research suggests that such an attentional maintenance bias in the early

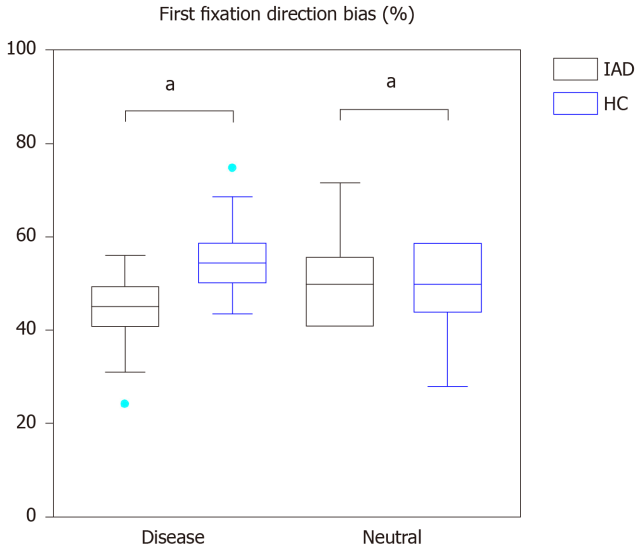


Figure 3 First-fixation direction bias of illness anxiety disorder and healthy subjects when presented with disease-related and neutral image pairs. HC: Healthy control; IAD: Illness anxiety disorder. $^{a}P < 0.05$.

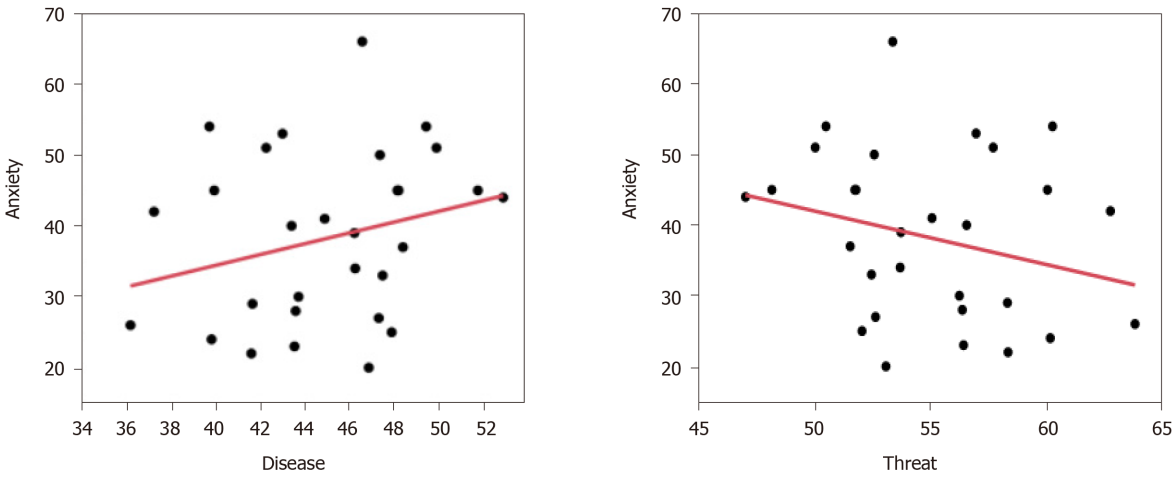


Figure 4 Total gaze duration to disease and threat in disease–threat image pairs.

attention stage may be due to the activation of disease-related schema within patients with IAD[31]. Attention schema theory suggests that if the threat stimulus is consistent with the schematic contents of an individual, then such stimulus is more likely to be processed. In addition, the activation of schemata leads to the allocation of more attentional resources to the threat stimulus at the late stage of strategic processing, manifesting as a greater frequency of selective attention. According to Salkovskis's cognitive-behavioral model of IAD, patients with IAD tend to overvalue illness-related information, giving it greater value and significance than reality, thereby inducing a cognitive bias such as selective attention. It is possible that illness-related information is more likely to activate the illness-related interpretation of the patients, leading to a longer processing period of such stimuli and the demonstration of a longer attention maintenance toward illness-related stimuli in the early maintenance stage.

At the late stage of attention, participants with IAD presented a noticeable avoidance of illness-related images, which was manifested as a shorter overall fixation duration on such pictures and a less overall fixation frequency. Therefore, the attentional pattern of patients with IAD was shown as an attentional avoidance bias toward illness-related images at the whole attention stage, but a delayed disengagement bias once attention captured by illness or threat information. The results demonstrate the attentional patterns of the participants when presented with illness-related, positive, and neutral stimuli. The findings revealed that patients with IAD showed different attentional patterns when presented with illness-related stimuli

and neutral stimuli. Specifically, patients showed an attentional maintenance bias in the early stage of attention and overall attentional avoidance toward illness symptom-related stimuli; however, they presented high levels of attention in the early attention stage and held their overall attentional maintenance when presented with normal stimuli (neutral information).

To further investigate the relationship between attention bias toward illness-related stimuli and the severity of symptoms among patients with IAD, this study utilized regression analysis. The results showed that the severity of anxiety symptoms had an impact on attention bias. In patients with mood disorder, there is a weakening of the ability to pay attention to the automatic processing of emotional information, resulting in defects and biases in the processing of emotional information[32]. Beck[33] believes that abnormal processing of emotional information in patients with mood disorders may be the main factor in the etiology of the disease and the maintenance of symptoms. Patients are sensitive to specific negative emotional information and alter their cognitive processing process, which may lead to symptom aggravation and maintenance. In many theories of clinical anxiety[19,34]. These attention biases have been regarded as initiating and maintaining clinical anxiety.

In 2009, Olatunji *et al*[35] proposed that the internal cognitive process indicates that IAD disorder may be related to anxiety disorder. The results also found that the more severe the anxiety symptoms, the more likely the disease stimulus attracts or occupies attention resources than other stimuli. Anxiety and IAD patients allocate excessive attention to disease information and struggle to dismiss the stimulus, showing delayed disengagement and attention bias; however, this feature is not obvious in their initial attentional stage.

Limitations and suggestions for future research

This study applied EM tracking technology to investigate attention biases of patients with IAD. Compared with past measurement methods based on participants' reactions, EM technology can effectively, directly, and continuously investigate the processing activities of attention of patients with IAD toward stimuli with threatening emotions, thereby differentiating the attention bias components more effectively. However, the method remains at the overt behavioral level and cannot analyze physiological parameters such as pupil changes and saccade during attentional processing. In addition, the method does not reveal the neurobiological mechanisms at play during attentional processing; hence, it is impossible to further explain the abnormality of brain function of patients with IAD. Future research is suggested to employ event-related potential technology (which has high time resolution) and functional magnetic resonance imaging technology (which has high spatial resolution) alongside eye-tracking technology to further investigate the characteristics of the attention bias and its mechanisms in patients with IAD. Furthermore, future study will use a machine learning classification method for the study to identify the IAD participants and estimate the accuracy of the eye-tracking method in identifying attention bias in patients with illness anxiety disorder.

CONCLUSION

Patients with IAD have an attention bias that is mainly manifested as an overall attentional avoidance when presented illness-related stimuli with disease, positive, and neutral stimuli, as well as avoidance of attention at the early attention stage; when presented with neutral stimuli, however, IAD performance showed higher delayed disengagement bias to illness and disease-related stimulus than in HCs. In addition, this study found that patients with suspected disorders with significant anxiety symptoms show attention bias in the late stage of attention processing, and struggle to dismiss the stimulus, showing delayed detachment. This study suggests that patients with IAD have attention bias and this may have provided a new way of identification of IAD symptoms using the eye-tracking evaluation method.

ARTICLE HIGHLIGHTS

Research background

Illness anxiety disorder (IAD) is a common, distressing, and debilitating condition with the key feature being a persistent conviction of the possibility of having one or

more serious or progressive physical disorders. Because eye movements (EMs) are guided by visual-spatial attention, eye-tracking technology is a comparatively direct, continuous measure of attention direction and speed when stimuli are oriented. Researchers have tried to identify selective visual attention biases by tracking EMs within dot-probe paradigms because the dot-probe paradigm can distinguish these attentional biases more clearly.

Research motivation

There are numerous studies that have investigated individuals with high social anxiety, generalized anxiety disorder, and depressive disorder, using EMs and a modified probe detection task to pictures of faces. However, no studies have provided an in-depth analysis of illness anxiety disorder using EMs.

Research objectives

Using the dot-probe paradigm, our primary aim in the current study was to explore the specificity of attention bias in IAD. In addition, we aimed to examine whether patients will display orienting attention biases, reflected by fixating first and more rapidly on illness stimuli than other alternatives.

Research methods

A case-control study design was used for the study, with the sample consisting of an IAD patient group and a healthy control (HC) group. Participants were recruited *via* e-mail and newspaper advertisement from Beijing An'Ding Hospital. The patient group fulfilled the criteria for IAD (DSM-5 and formerly named hypochondriasis in DSM-4) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). The stimuli used in the dot-probe task consisted of 128 pictures including 35 pictures from China internet sources, and 93 pictures selected from the International Affective Pictures System, which were grouped into four main categories: Illness-related, social threat, positive, and neutral pictures. These pictures were used to assess attentional bias in IAD patients. All four EM indicators were statistically analyzed using independent sample *t*-test. The differences between IAD group and HC group were compared on different types of images. The mean value of the group was compared with that of independent samples test, and $P < 0.05$ indicated that the difference was statistically significant.

Research results

When presented with disease-related images, the first-fixation direction of the IAD group was lower than that of the HC group ($t = -2.467$, $P = 0.017$); while presented with neutral images, it was higher than that of HC group ($t = 2.467$, $P = 0.017$). When the participants were presented with the disease–neutral image pairs, independent sample *t*-test found that the first-fixation duration of the IAD group (280.476 ± 55.154) for the disease picture was significantly greater than that of the HC group (252.807 ± 45.075) ($t = 2.128$, $P = 0.038$). When the participants were presented with the disease–social threat image pairs, independent sample *t*-test found that the first-fixation duration of the IAD group (281.20 ± 61.472) for the disease picture was significantly greater than that of the HC group (246.40 ± 30.991; $t = 2.769$, $P = 0.008$). There was also a difference in the social threat picture (IAD group: 296.86 ± 58.129, HC group: 266.37 ± 40.172; $t = 2.363$, $P = 0.022$). Independent sample *t*-test showed the overall fixation frequency bias toward the disease images in the IAD group was higher than in the HC group ($t = 1.841$, $P = 0.071$), and fixation frequency bias toward the positive images was lower than in the HC group ($t = -1.841$, $P = 0.071$).

Research conclusions

Patients with IAD have an attention bias that is mainly manifested as an overall attentional avoidance when presented illness-related stimuli with disease, positive, and neutral stimuli, as well as avoidance of attention at the early attention stage when presented with neutral stimuli; however, IAD performance showed higher delayed disengagement bias to illness and disease-related stimulus than did the HCs. In addition, this study found that patients with suspected disorders with significant anxiety symptoms show attention bias in the late stage of attention processing, and struggle to dismiss the stimulus, showing delayed detachment.

Research perspectives

This study suggests that patients with IAD have attention bias and this may have provided a new way of identifying IAD symptoms using the eye-tracking evaluation

method.

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7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 April 19; 11(4): 87-152



Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJP* as 3.545; IF without journal self cites: 3.545; Ranking: 46 among 155 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
April 19, 2021

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INSTRUCTIONS TO AUTHORS
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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 April 19; 11(4): 87-93

DOI: 10.5498/wjp.v11.i4.87

ISSN 2220-3206 (online)

OPINION REVIEW

Contemplative sciences: A future beyond mindfulness

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Author contributions: García-Campayo J and Navarro-Gil M contributed to the conceptualization; García-Campayo J and López del Hoyo Y contributed to the original draft preparation; García-Campayo J and Navarro-Gil M contributed to the review and editing; all authors have read and agreed to the published version of the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

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Manuscript source: Invited

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Abstract

Mindfulness is a psychological technique based on Eastern meditative practices that was developed in the late 1970s by Kabat-Zinn at the University of Massachusetts. Initially, there was a debate over whether it should be considered a scientific technique or labelled as part of the "new wave" practices. Today, mindfulness is omnipresent in modern societies but has suffered from merchandising and banalization, which has been strongly criticized. Despite some limitations regarding methodological aspects of mindfulness research, it is considered effective for treating many physical and psychological disorders, and even it is recommended in clinical guidelines such the British National Institute for Health and Care Excellence. During the last 2500 years, mindfulness practices have moved from Northern India across most of Asia, but their mixing with Western science and culture at the end of the 20th century is considered a key event in recent history. For the first time in human history, due to globalization, the wisdom of all contemplative traditions can be shared with all human beings and assessed by science. Mindfulness practices, yoga included, are giving birth to a new field of knowledge, contemplative sciences, which go beyond mindfulness and is devoted to helping humanity to reach higher levels of happiness and mental peace.

Key Words: Contemplative sciences; Mindfulness; Meditation; Compassion; Psychotherapy; Wellness

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Core Tip: This paper reflects on the following subjects: (1) The efficacy and expansion of mindfulness in modern world-limitations from a scientific and a philosophical

manuscript

Specialty type: Psychiatry

Country/Territory of origin: Spain

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 20, 2021
Peer-review started: January 20, 2021
First decision: February 15, 2021
Revised: March 2, 2021
Accepted: April 5, 2021
Article in press: April 5, 2021
Published online: April 19, 2021

P-Reviewer: Hulke SM
S-Editor: Zhang H
L-Editor: A
P-Editor: Li JH

perspective; (2) The exciting times we are entering as a consequence of the marriage between science and contemplative techniques; and (3) Finally, the consequence of all these aspects–the birth of a new field of knowledge, the contemplative sciences, which includes mindfulness. They will offer humankind the wisdom of centuries of deep knowledge to facilitate the highest levels of happiness and connection imaginable.

Citation: Garcia-Campayo J, López del Hoyo Y, Navarro-Gil M. Contemplative sciences: A future beyond mindfulness. *World J Psychiatr* 2021; 11(4): 87-93
URL: https://www.wjgnet.com/2220-3206/full/v11/i4/87.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i4.87

INTRODUCTION

Concept and origin of mindfulness

Mindfulness practice involves developing the skill of directing one's attention to whatever is happening in the present moment[1]. According to Kabat-Zinn[2], "mindfulness is the practice of purposely bringing one's attention to experiences occurring in the present moment without judgment", a skill that can be developed through attentional meditation or other training. As noted by Brown *et al*[3], definitions of mindfulness are typically selectively interpreted based on who is studying them and how they are applied. Some have viewed mindfulness as a mental state, while others have considered it as a set of skills and techniques.

The Buddhist term translated into English as "mindfulness" originates in the Pali term *sati* and in its Sanskrit counterpart *smrti*, and it is a significant element of Buddhist traditions[4]. It is often translated as "bare attention", but in Buddhist texts, it has a broader meaning and application and can also be defined as "memory" or "recollection"[5]. *Sati* is one of the seven factors of Enlightenment, and "correct" or "right" mindfulness is the seventh element of the Noble Eightfold Path, the main teaching in this religion.

Jon Kabat-Zinn started to teach mindfulness in September 1979 at a hospital associated with the University of Massachusetts. This was the beginning of mindfulness in the West. The program was called the "Stress Reduction and Relaxation Program". He tried to bring his Buddhist practice together with his work life as one unified whole in the service of something useful[2]. Some months before, in a two-week *vipassana* retreat, he had experienced a "vision" about mindfulness that impressed him. In his own words, in the vision, he saw not only a model that could be put in place but also the long-term implications of the implementation of mindfulness across the world[1]. During the 1980s, Kabat-Zinn's main worry was to avoid mindfulness being labelled a "hippy" or "new age" practice, and for that reason, he eliminated any Buddhist terminology and focused on its medical benefits and the importance of being assessed by scientific research[2]. Today, mindfulness has become part of modern society's mainstream way of life[6], and it is considered the next revolution in public health[7].

EFFICACY OF MINDFULNESS

In the last 20 years, meta-analyses have demonstrated the utility of mindfulness for increasing psychological and physical wellbeing in healthy adults in general[8] and in specific environments such as the workplace[9] or school[10]. As a treatment, it has demonstrated efficacy in the treatment of mental disorders[11], some relevant studies are summarized in Table 1.

Mindfulness seems useful across all age ranges from, for example, adolescents[12] to middle-aged military veterans[13].

Regarding medical conditions, meta-analyses confirm the efficacy of mindfulness in treating cancer in general[14] and more specifically in treating breast cancer[15], pain[16], hypertension[17], diabetes[18], rheumatoid arthritis[19] and many other disorders.

Overall, the maximum efficacy of mindfulness as a treatment has been found in treating recurrent depression[20], and this is the reason the British Clinical Guide

Table 1 Efficacy demonstrated of mindfulness as treatment in different mental disorders

Mental disorder	Ref.
Depression and anxiety	Hofmann *et al*[39]
	Blanck *et al*[40]
	Godfrin *et al*[41]
Subtance and behavioural addictions	Sancho *et al*[42]
	Glasner *et al*[43]
Schizophrenia	Hodann-Caudevilla *et al*[44]
	Chien *et al*[45]

National Institute for Health and Care Excellence[21] recommends mindfulness, considering it the psychological treatment of choice.

However, some authors[22] have argued that published data about the efficacy of mindfulness may be oversized and that the authors of mindfulness studies may be biased and more focused on positive outcomes than on negative outcomes. In this sense, the harshest criticism of the scientific evidence regarding the benefits of mindfulness was the paper of Van Dam *et al*[23], which described the relevant methodological limitations in the research on this technique. This article was responded to by prominent researchers in the field[24], who affirmed that those limitations are commonplace for all psychological therapies and, even more important in our opinion, that mindfulness, as part of a contemplative tradition, was not developed specifically for treating human disorders but was created to improve human wellbeing and flourishing, and this is the point I would like to emphasize in this article.

LONG JOURNEY OF MINDFULNESS IN THE WEST

Mindfulness, as the core teaching of Buddhism, has travelled a long journey from its original homeland in Northeast India. Early on, it travelled to the island of Sri Lanka; centuries later, it spread to the river basins of southeast Asia, then to monasteries in the mountains of China, Korea and Japan, and on to the hidden kingdoms of the Himalayas. Across the centuries and these countries, mindfulness had to adapt to the characteristics of the people who lived there and incorporated their wisdom. However, the last stage in this journey, the growth into Western countries, has produced unparalleled consequences. According to the prestigious British historian Toynbee[25], the arrival of Buddhism in the West was the single most important fact during the 20th century, as it allowed meditation to become part of mainstream Western culture.

As a consequence, mindfulness has had to be assessed by science and demonstrated to be efficacious in different environments. At present, mindfulness has moved from its traditional settings of peaceful Buddhist monasteries and is now practiced in developed and secularized cities inhabited by people eager for pragmatic results. People who transmit these teachings are no longer venerable old meditation masters followed by groups of disciples but are instead university lecturers holding degrees in psychology or medicine. Mindfulness is used not to obtain freedom from the cycle of birth and death but to liberate people from the strains of stressful relationships, mental diseases and the worries of daily life.

This new model of understanding mindfulness has been severely criticized as the so-called "McMindfulness" movement[26]. Critics have called out the indiscriminate use of mindfulness decontextualized from the original Buddhist teachings from in which it originated and its employment in different settings. Mindfulness meditation has become so popular that many products and merchandising practices use this name. For example, the trendy fitness apparel company Lululemon is now advertising mindfulness clothing for men. There are also products called Mindful Meats and Mindful Mints, and Sherwin-Williams sells a paint colour they call Mindful Gray[27]. Mindfulness is said to be a $4B industry. More than 60000 books for sale on Amazon have a variant of "mindfulness" in their title and tout the benefits of mindful parenting, mindful eating, mindful teaching, mindful therapy, mindful leadership, mindful finance, mindful nations, and mindful dog owners, to name just a few[28].

This oversimplification also occurs in scientific research: There is a danger that the wisdom of Eastern contemplative traditions might be reduced to a matter of gaining certain skills such as attention, memory or emotion regulation. Alternatively, based on materialistic premises, the efficacy of mindful practices could be reductively explained exclusively on the basis of neurophysiology[5].

UNBELIEVABLE HISTORICAL PERIOD IN WHICH WE LIVE

The beginning of the 21st century is probably one of the most fascinating periods in human history. Many masters of contemplative traditions are teaching mindfulness as a way to reach a wider range of people. Most long-term mindfulness instructors embrace spiritual teachings, as mindfulness is not able to provide answers to the deepest questions of existence.

Today, online technologies and cheap travel around the world have facilitated a level of globalization that makes it possible to receive teachings from great masters from different countries. This was impossible centuries ago, and a disciple had to choose one only master and remain with that master for years. Now, the immediate interchanging of ideas and the dissemination of teachings considered secret for generations are accelerating human knowledge acquisition. In addition, the marriage of science and contemplative wisdom allows us to examine the impact of traditional meditative techniques and the changes they produce in the human brain and body.

CONTEMPLATIVE SCIENCES

In his 1930 book "Civilization and Its Discontents", Freud advocated for the need for a new and secular science of psychotherapy as a pragmatic alternative to the traditional healing techniques offered by religions. Since then, Western psychology/psychiatry has operated separately from religion[29]. However, in recent years, robust research has confirmed the therapeutic and wellbeing potential of qualities such as love, compassion and altruism[30-33]. For this reason, conventional psychology is moving towards contemplative science, which has always been considered non-scientific knowledge. Recent studies have confirmed, for instance, that Tibetan monks can voluntarily self-generate high-frequency gamma synchrony[34] and that mindfulness meditation increases thickness in the prefrontal and insular cortex[35]. Yoga, a group of physical, mental, and spiritual practices originated in ancient India, has also demonstrated a great efficacy in improving mental well-being[36], and is considered a relevant component of the contemplative sciences. These and other research studies have placed meditation at the axis of contemplative science and have emphasized brain neuroplasticity.

These developments in the field of psychology gave birth to the so-called contemplative sciences movement some years ago. Many experts believe that mindfulness has demonstrated to be effective and that a wider theoretical frame is necessary. Davidson *et al*[37] coined the term "contemplative neuroscience", which describes the emerging field arising at the intersection of meditation research and neuroscience. It includes any kind of meditation, yoga, mantra recitation, intensive breathing or healing movement[38]. This new science fulfils the dream of visionary pioneers in psychiatry and psychology, such as Carl Gustav Jung and Ken Wilber, and is connected to some aspects of transpersonal psychology. Several universities across the world have developed courses on or departments for on contemplative sciences or similar disciplines, some examples including Brown University (Providence, Rhode Island), the University of San Diego (San Diego, California), Naropa University (Boulder, Colorado) or the University of Mary Washington (Fredericksburg, Virginia) in the United States and Ottawa in Canada.

CONCLUSION

Future of mindfulness

I envision the future of mindfulness and related disciplines like a millennial wisdom tree with two main branches. In the first, mindfulness will develop with an instrumental aim. Its objective will be to relieve the mental and physical suffering of ill people and to increase the wellbeing of healthy persons in everyday life and in every

challenging environment they live in. However, in addition to mindfulness, there will be a second branch, contemplative sciences. This branch will be devoted to allowing humanity to experience the highest level of everlasting happiness that humankind can enjoy, regardless of external circumstances, which is linked to understanding the ultimate reality.

ACKNOWLEDGEMENTS

The authors are grateful to the Contemplative Sciences Chair for his support in the publication of this paper.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 April 19; 11(4): 94-108

DOI: 10.5498/wjp.v11.i4.94

ISSN 2220-3206 (online)

REVIEW

Global health disparities in vulnerable populations of psychiatric patients during the COVID-19 pandemic

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Author contributions: Diaz A conceptualized this paper, draft the initial manuscript, reviewed and revised the manuscript; Baweja R and Bonatakis JK contributed in the initial manuscript, reviewed and revised the manuscript; Baweja R conceptualized this paper, contributed in the initial manuscript, critically reviewed and revised the manuscript; all authors approved the final manuscript as submitted and agree to accountable for all aspect of the work.

Conflict-of-interest statement: All authors report no conflicts of interest related to the subject of this article.

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Abstract

The coronavirus disease 2019 pandemic affects psychiatric patients disproportionately compared to the general population. In this narrative review, we examine the impact of the pandemic on significant global health disparities affecting vulnerable populations of psychiatric patients: People of diverse ethnic background and color, children with disabilities, sexual and gender minorities, pregnant women, mature adults, and those patients living in urban and rural communities. The identified disparities cause worsened mental health outcomes placing psychiatric patients at higher risk for depression, anxiety and posttraumatic stress disorder symptoms. Those psychiatric patients who are ethnic minorities display barriers to care, including collective trauma and structural racism. Sexual and gender minorities with mental illness face discrimination and limited access to treatment. Pregnant women with psychiatric diagnoses show higher exposure to domestic violence. Children with disabilities face a higher risk of worsening behavior. Mature adults with psychiatric problems show depression due to social isolation. Psychiatric patients who live in urban communities face pollutants and overcrowding compared to those living in rural communities, which face limited access to telehealth services. We suggest that social programs that decrease discrimination, enhance communal resilience, and help overcome systemic barriers of care should be developed to decrease global health disparities in vulnerable population.

Key Words: COVID-19; Pandemic; Health disparities; Global disparities; Mental health disparities; Access to care

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 17, 2021
Peer-review started: February 17, 2021
First decision: March 16, 2021
Revised: March 30, 2021
Accepted: April 5, 2021
Article in press: April 5, 2021
Published online: April 19, 2021

P-Reviewer: Liu HQ, Roslan NS
S-Editor: Gong ZM
L-Editor: A
P-Editor: Li JH



Core Tip: During the coronavirus disease 2019 (COVID-19) pandemic, many psychiatric patients encounter limited access to care due to major health disparities. In this minireview, we examine the impact of the COVID-19 pandemic on vulnerable psychiatric populations due to ethnic-racial disparities, disparities involving children with disabilities, the role of sex and gender trauma in the mental health in sexual and gender minorities, disparities among pregnant women, disparities among mature adults, and the impact in urban *vs* rural populations.

Citation: Diaz A, Baweja R, Bonatakis JK, Baweja R. Global health disparities in vulnerable populations of psychiatric patients during the COVID-19 pandemic. *World J Psychiatr* 2021; 11(4): 94-108
URL: https://www.wjgnet.com/2220-3206/full/v11/i4/94.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i4.94

INTRODUCTION

Amid the coronavirus disease 2019 (COVID-19) pandemic, vulnerable populations are the most affected medically, resulting in limited access to care and worsened health outcomes, including death[1]. Identified vulnerable populations include children with developmental disabilities, mature adults, pregnant women, sexual and gender minorities, and Black, Indigenous and People of Color communities[2-6]. Health outcomes differ in vulnerable populations than the general public since there is a disproportionate exposure to risk factors that cause disease[7]. Among these vulnerable groups, patients with pre-existing psychiatric conditions pose an increased risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, which causes the respiratory state known as COVID-19 illness[8]. Psychiatric patients tend to have higher comorbid medical conditions, such as diabetes mellitus and hypertension, which predispose to disease[8,9]. Isolation and small social networks limit support from friends and families during prolonged periods of quarantine[10,11]. Psychiatric patients may display inadequate social space and limited adherence to personal protection strategies such as handwashing or the use of a mask on a consistent basis[12].

Unprecedented financial stressors due to loss of jobs, limited access to adequate housing, and a higher risk of homelessness can further affect mental health care access[13]. In an ongoing study by the Center for Disease Control and Prevention in the United States, up to 12% of individuals in the general population responded that they needed counseling and medication for mental health but could not receive it during the pandemic[14]. Delays in treatment affected primarily unemployed individuals due to fears of contamination with COVID-19 when assisting appointments[15]. Most importantly, the COVID-19 pandemic disrupted mental health services globally. The World Health Organization surveyed 130 countries and over 60% reported impacts in mental health care services, including children (72%), older adults (70%), and women requiring prenatal and postnatal services (61%)[16].

Psychiatric patients in vulnerable populations are also at increased risk for mitochondrial stress, which potentially can result in an altered immune response to COVID-19 illness[17]. Mitochondria are particularly susceptible to dysfunction affected by nutrition and viral disease exposure[17]. It is posited that mitochondrial stress can eventually widen the health disparity since many vulnerable populations live in urban environments affected by toxic metal pollution[17]. Overcrowded housing, inadequate nutrition, socioeconomic stressors, age, and metabolic syndrome can further potentiate the effect of mitochondrial stress in vulnerable populations affected by COVID-19 illness[17,18].

The disparity of vulnerable populations can further be attributed to immune perturbations associated with stress that precede pro-inflammatory responses, especially in Black, Indigenous and People of Color[19]. Before the COVID-19 pandemic, these vulnerable populations lived in a heightened state of physiological stress and awareness complicated by psychological stress due to socioeconomic and environmental stressors[19]. The mechanism in which SARS-CoV-2 extends to the central nervous system is binding to peripheral nerve terminals and through retrograde transport reaching the brain[12,20,21]. The SARS-CoV-2 can also impact the central nervous system through a systemic cytokine response resulting in further

chronic inflammation and, in some cases, brain damage and even death[20,21]. Among psychiatric patients, the immune response triggered by COVID-19 may lead to depressed mood, severe anxiety, and suicidal ideations[9].

Apart from COVID-19 causing neurotropism and disarray of reactive immune responses, there is an increased risk for collective trauma in vulnerable populations[12,22]. COVID-19 is most likely to impact the mental health of psychiatric patients compared to healthy controls with a higher incidence of posttraumatic stress disorder (PTSD) (31.6% *vs* 13.8% controls)[9]. The collective trauma response is multilayered and consists of three components: Further fears of infection, prevalent economic difficulties, and disruption of established routines with isolation[22,23]. COVID-19 disproportionately affects vulnerable ethnic populations contributing to an accumulation of trauma through experiences of racism, discrimination, and social inequalities[22,24]. The COVID-19 pandemic forms a feedback loop between viral illness and disparities, leading to the accumulation of further inequities comprising a collective trauma[22].

Preceding the COVID-19 pandemic, the average untreated global rates of schizophrenia, major depressive disorder, and alcohol use disorder were 32.2%, 56.3%, and 78.1%, respectively[25]. These untreated psychiatric illnesses could potentially overburden an existing overwhelmed health care system, further increasing the inequalities in health between groups of people in countries, thus causing global health disparities[26]. Although there is a growing body of evidence of the mental health impact on the global population during the COVID-19 pandemic[27], little is known about the effects of COVID-19 in vulnerable psychiatric patients. In this minireview, we highlight the global health disparities affecting vulnerable psychiatric populations (Table 1) and examine the social barriers influencing global mental health care during the COVID-19 pandemic.

METHODS

Search engines through PubMed, Google Scholar, and PsychINFO were used with the following keywords: COVID-19, global health disparities, global mental health disparities, social barriers, social determinants of health, ethnic health disparities, sexual gender minorities, pregnant women, psychiatric patients, children, mature adults, developmental disabilities, urban and rural population. Articles in English and articles translated in English were reviewed from January 2020 to March 2021.

ETHNIC DISPARITIES

Psychiatric patients from ethnic minorities display worsened mental health outcomes during the COVID-19 pandemic. In the United Kingdom, people of color (Bangladeshi, Indian, and Pakistani men) show a more significant increase in mental health distress than White British men[28]. In the United States, ethnic minority respondents who reported prior treatment for depression, anxiety, and PTSD presented with higher prevalence of these symptoms and subsequent adverse mental health outcomes than those who did not receive treatment[29].

It is speculated that Blacks may have fewer physiological and psychiatric complications from COVID-19 based on a reduced molecular expression of angiotensin-converting enzyme-2, the binding site for SARS-CoV-2 present in the lung, kidneys, and brain[30]. However, there is a notable difference in COVID-19 outcomes since studies have shown more complications to the viral illness, including higher psychological distress and increased mortality in Blacks compared to Whites[31,32]. In the United States, a third of hospitalized COVID-19 patients are Black, although they make up only 13% of the total population[33]. In the United Kingdom, Blacks were found to have a four-fold increased risk for COVID-19 infection[31]. Black individuals diagnosed with COVID-19 (34.6%) showed psychological distress, but only a minimal (8.6%) sought out psychiatric care[31]. Poor access to services, stigma, cultural insensitivity and lack of awareness of their symptoms might prevent Blacks from obtaining mental health care during traumatic events[34].

Structural racism or the "ways in which societies foster discrimination through mutually reinforcing inequitable systems[35]" can complicate mental health disparities. A general mistrust of health systems is based on the historical mistreatment of Blacks in psychiatric care[36]. To this extent, the American Psychiatric Association issued a public apology about their role in Blacks' historical injustices acknowledging their

Table 1 Review of primary literature on coronavirus disease 2019 global health disparities

Ref.	Vulnerable population	Type of study	Country or region	Key mental health findings
El Hayek *et al*[5], 2020	Mature adults	Thirteen country case studies by thirteen early career psychiatrists	Arab Countries in the Middle East North Africa Region	General lack of mental health services for geriatric population during the COVID-19 pandemic
Proto and Quintana-Domeque[28], 2021	Ethnic minorities	Longitudinal survey	United Kingdom	Bangladeshi, Pakistani, and Indian individuals experienced significant increase in mental health distress than general population
Czeisler *et al*[29], 2020	Ethnic minorities	Cross sectional survey	United States	Significant higher suicide rates in ethnic minorities having considered suicide in the past 30 d before completing survey during COVID-19 pandemic
Lassale *et al*[31], 2020	Ethnic minorities	Cohort study	United Kingdom	Greater psychological distress experienced by Asians after hospitalization for COVID-19 than general population
Newby *et al*[39], 2020	Ethnic minorities	Longitudinal survey	Australia	Significant higher anxiety and distress in individuals with self-reported history of mental health diagnosis than those without a mental health diagnosis
Lee and Waters[45], 2020	Ethnic minorities	Longitudinal survey	United States	Over 40% of Asian Americans reported increase in anxiety, depressive symptoms and sleep difficulties during the COVID-19 pandemic
Gómez-Ramiro *et al*[54], 2020	Children with autism and developmental disorders	Retrospective study	Spain	Significant increase in acute psychiatric hospitalizations during COVID-19 lockdown
Nadler *et al*[65], 2021	Children with autism and developmental disorders	Case study	United States	Case study of child with autism and behavioral health concerns examines limited psychosocial support and availability during the COVID-19 pandemic
Bishop[69], 2020	Sexual gender minorities	Qualitative study	Global	Interviews with 59 SGM from 38 countries; majority showed increased isolation and anxiety
Suen *et al*[73], 2020	Sexual gender minorities	Community based survey	Hong Kong (China)	SGM are particularly vulnerable to poor mental health outcomes during the COVID-19 pandemic
Peterson *et al*[74], 2020	Sexual gender minorities	Cross sectional, convenience sample survey	United States	Greater psychological distress in SGM. A large number of bisexual individuals in the sample may have magnified the differences between SGM and sexual-majority groups
Durankuş and Aksu[77], 2020	Pregnant women	Cross sectional survey	Turkey	Higher depression scores on Edinburgh Postpartum Depression Scale in pregnant women than control group during COVID-19 pandemic
Liu *et al*[80], 2021	Pregnant women	Cross sectional survey	United States	Study on pregnant women and women who recently gave birth. Women with self-reported psychiatric diagnoses were 1.6-to-3.7 more likely to score at clinically significant levels of depression, generalized anxiety, and PTSD
Corbett *et al*[81], 2020	Pregnant women	Preliminary cross-sectional survey	Ireland	Pregnant women surveyed described heightened anxiety over COVID-19 affecting older adults, their children and their unborn baby
Saccone *et al*[82], 2020	Pregnant women	Cross sectional survey	Italy	More than half of pregnant respondents rated psychological impact of COVID-19 as severe
Wang *et al*[83], 2020	Female gender	Cross sectional survey	China	Increased psychological impact on female gender and having a poor self-rated health status
Liu *et al*[85], 2020	Female gender	Cross sectional survey	China	Female respondents had higher negative cognitions on posttraumatic stress symptoms than males
Berthelot *et al*[87], 2020	Pregnant women	Longitudinal cohort survey	Canada	Pregnant women assessed during the COVID-19 pandemic reported more prenatal stress and psychiatric symptoms than pre-pandemic cohort
Lebel *et al*[88], 2020	Pregnant women	Cross sectional survey	Canada	Higher symptoms of depression and anxiety in pregnant women were associated with greater concern about COVID-19 threatening the life of the mother and baby
Taquet *et al*[113], 2021	Psychiatric *vs* non psychiatric population	Retrospective medical record network study	United States	Psychiatric diagnosis might be considered an independent risk factor for COVID-19 illness.
Logue *et al*[114], 2021	Psychiatric *vs* non psychiatric population	Longitudinal prospective cohort survey	United States	2.3% of respondents reported "brain fog" at 6 mo post COVID-19 infection

COVID-19: Coronavirus disease 2019; PTSD: Posttraumatic stress disorder; SGM: Sexual and gender minorities.

influence in inequitable practices, including the misdiagnosis of schizophrenia in this population[37].

Indigenous people also face similar mental health disparities. There are presently 45 million indigenous people living in Latin America, 5.2 million in the United States, 2 million in Canada, and 798363 Aboriginal or Torres Strait Islander living in Australia[38]. In a controlled variable study, being Aboriginal or Torres Strait Islander was a strong predictor for higher anxiety, suggesting that indigenous people in Australia might be more vulnerable to poorer mental health outcomes[39]. During the COVID-19 pandemic, many indigenous people tend to handle stress independently of others by relying on spirituality to guide them, leading to a decline in seeking mental health care services[40].

Limited access to indigenous villages due to isolation in remote geographical areas can prevent obtaining mental health care for indigenous people. In Brazil, many indigenous people cannot access health services due to geographical distance and unavailability of care[41]. Restrictive bans placed by governments to prevent the pandemic's spread can further complicate travel by health care workers to these remote places[38]. In specific indigenous communities such as the First Nations, Inuit, and Métis in Canada, there have been lower rates of COVID-19 compared to non-indigenous people due to protective measures taken by their leaders[42]. Despite lower infection and mortality in Canadian indigenous cultures, 38% of indigenous people reported fair to poor mental health on a governmental online survey during the pandemic compared to 16% in prior years[43].

Public health messaging, which is essential during a pandemic, is hindered by poor access to broadband and internet service in indigenous villages. In Mexico, only 10% of indigenous villagers in Oaxaca have adequate internet service, mostly concentrated in city centers[44]. Limited access to internet service hampers the growth of telepsychiatry modalities in these communities, which could be beneficial for patient treatment.

Although the scientific literature focuses mainly on Blacks and their experience with discrimination during the COVID-19 pandemic, Asians have been significantly affected, displaying in some cases worsened mental health outcomes[45]. In the United Kingdom, 41.7% of hospitalized Asians with COVID-19 proved to have higher depression screening symptoms on Patient Health Questionnaire 4 than Blacks[31]. In the United States, many Asian Americans are targeted by their ethnicity in response to reports of the emerging virus[45]. Compared to pre-pandemic percentages, a United States cross-sectional study showed that 41% of Asians and Asian Americans reported an increase in anxiety and that 53% reported an increase in depressive symptoms[45]. A higher level of community support mitigates the impact of discrimination on depressive symptoms in Asians and Asian Americans[45]. Among other ethnic minority groups, Asians showed a lower incidence of suicide (6%) in the United States[29].

During the start of the pandemic, Hispanics displayed a higher incidence of suicidal thoughts (18.6%), higher anxiety and depressive symptoms compared to other ethnic groups in the United States[29]. In general, Hispanics have lower utilization of mental health services with a strong Spanish language social preference and higher levels of ethnic identity, which are strong predictors for mood and anxiety disorders[46]. Hispanics also have the lowest health insurance coverage rate and twice the poverty level than Whites in the United States[47]. This ethnic group is overrepresented in critical essential workers, which, during the pandemic, mainly worked in the food industry, laboring in overcrowded meatpacking factories with poor ventilation, thus increasing exposure to COVID-19 illness[29,48].

Among other ethnic minorities, cultural-religious minorities have shown worsened mental health outcomes during the COVID-19 pandemic. For instance, in India, an increased relapse of pre-existing psychiatric illness was observed during the quarantine period in Kashmir Muslims already affected by trauma and civil unrest in the area[49]. Moreover, members of the religious majority discriminated against the Muslim community in social media posts as being spreaders of viral illness[49].

DISPARITIES IN CHILDREN WITH DEVELOPMENTAL DISABILITIES

Children, adolescents, and adults with intellectual disability (ID) and neurodevelo-

pmental disorders like autism spectrum disorder (ASD) are vulnerable to significant impacts by pandemic-related changes such as social distancing standards, stay-at-home orders, and closures of nonessential services. Furthermore, many individuals with ID and ASD experience significant communication challenges in processing information[50], afflicting their ability to respond effectively and efficiently to social changes implemented secondary to the COVID-19 pandemic. Given expressive communication challenges, individuals with ID or ASD may have difficulty communicating emotional distress, pain, or illness symptoms[51]. As a result, many individuals with ID and ASD have to rely on their families or caregivers to communicate important information about the pandemic or observe for symptoms of a potential viral illness. Caregiver stress and depression increased during the COVID-19 pandemic compared to the pre-pandemic outbreak furthering the mental health disparity[52]. Furthermore, individuals with ID and neurodevelopmental disorders face various challenges secondary to the pandemic, including limited access to behavioral health services, changes in health services delivery, disruption of educational services, and vocational changes[53]. During the lockdown period in Spain, there were increased psychiatric emergency admissions in individuals with ASD, most likely due to an observed disruption of family daily routines[54].

Individuals with ASD share a physiological and genetic vulnerability for COVID-19. There are documented increased levels of pro-inflammatory cytokines present in individuals with ASD[55]. The tendency towards a pro-inflammatory state among individuals with ASD may place them at higher risk for even more severe symptoms once this virus is contracted[56], including a rare multisystemic inflammatory syndrome evident in children[57]. Focal brain inflammation in the amygdala with activation of mast cells may potentially result in a higher prevalence of ASD diagnoses due to COVID-19 infection[58]. Furthermore, individuals with ID and ASD have a greater risk for overall poor health compared to the general population[59], type 2 diabetes[60], along with sensory impairments and physical disabilities[61]; all of these have been documented as poor prognostic risk factors from COVID-19 infection[62].

Many individuals with ID and ASD share documented health disparities both in the pre-pandemic and pandemic period. This health disparity might be due in part to the higher rates of ASD among transgender and gender-diverse individuals *vs* cis-gender individuals[63]. In the pre-pandemic period, transgender and gender-diverse groups with ASD experienced increasing rates of comorbid mental illness and higher rates of being refused health services[64]. In the United States, access to existing therapeutic services, including Applied Behavioral Analysis in rural regions, has been curtailed due to job shortages[65]. In addition to disparities in medical access and services contributing to this disproportion, there is evidence about potential genetic or biological susceptibilities among various ethnic groups[66]. It could be expected that individuals with ID and ASD within these groups carry even higher risk given the vulnerabilities outlined above.

SEXUAL AND GENDER DISPARITIES

Sexual and gender minorities (SGM) include Lesbian, Gay, Bisexual, Transgender, Two-Spirit, Queer, Questioning, Intersex, and Asexual (LGBT2SQIA+) individuals[67]. SGM are a diverse group whose history of stigma, systemic discrimination, and structural violence leaves them particularly vulnerable to disproportionate impact by COVID-19 given inequitable conditions that have reduced their access to vital resources[67]. SGM share a heightened psychological vulnerability associated with minority stress, which increases their susceptibility to underlying health conditions[22,68]. Historically, SGM have been excluded from disaster research, thereby preventing identification of their unique mental health needs[69,70]. It is, therefore, no surprise that SGM experience health disparities, including higher rates of mental health diagnoses, substance use, and suicidality compared to their sexual-majority counterparts[71].

Due to discrimination, SGM are overrepresented in essential services and sex work, experience higher poverty rates than the general population, and are less likely to have adequate healthcare and are more vulnerable to poor mental health outcomes[72,73]. When SGM intersect with oppressed intersections of identity, such as race, ethnicity, socioeconomic status, or chronic illness, the compounding nature of these vulnerabilities creates even wider health disparities for communities of SGM[68,70,72]. For instance, a Hong Kong community sample found stressors beyond those of the COVID-19 pandemic, including family conflict due to sexual orientation and

disconnection to the SGM community, likely leading to a combined effect on the one-week prevalence of clinical depression (31.5%) and generalized anxiety disorder (27.9%)[73]. Given the social disadvantages and mental and physical health disparities faced by SGM, it is likely that the pandemic trauma and social isolation measures to mitigate COVID-19 transmission are exacerbating these inequalities[68].

Discrimination, oppression, and violence occur at the familial level, making isolation and quarantine dangerous for SGM who are forced to cohabitate with unsupportive and abusive family members or partners[69]. Many SGM rely upon community supports for safety and acceptance, yet due to COVID-related restrictions, SGM have been unable to connect with their supportive community safe spaces[69]. SGM experience more anxiety, depression, and peritraumatic stress responses while doubling the odds of meeting future criteria for COVID-related PTSD when compared to sexual majorities[74].

Furthermore, given the higher rates of human immunodeficiency virus (HIV), mental health diagnoses, substance use, and trauma among SGM, disruptions in mental healthcare access during COVID-19 have been particularly concerning[69,73,75]. SGM reported having difficulty obtaining HIV medications and mental health care in case studies in 59 countries[69]. Further validating this report, a convenience sample (n = 2732) of cisgender gay men and other men who have sex with men across 103 countries displayed moderate to severe psychological distress with a prevalence of 31% in depression[75]. Globally, SGM have reported that they would delay or avoid seeking care for COVID-19 symptoms due to anticipated stigma and discrimination[69].

DISPARITIES IN PREGNANT WOMEN

Pregnant women are a vulnerable group for COVID-19 due to an increased risk of physical and mental health complications, such as depression and anxiety[76,77]. Homeschooling children and taking care of elderly family members in addition to working from home has been a challenge for most women, which generally increases caregiver stress[78]. COVID-19-related health anxiety experiences may also increase the likelihood of mental health symptoms among those pregnant women without a previous psychiatric diagnosis[79]. Pregnant women in Ireland reported excessive worries regarding older relatives and their unborn baby[80], while Italian pregnant women reported high rates of anxiety regarding vertical transmission[81]. Studies from China, when COVID-19 emerged, have found that the female gender is significantly associated with higher self-reported anxiety, depression, and posttraumatic stress, causing a severe overall psychological impact[82-85]. Similarly, studies from Canada reported a higher rate of depressive and anxiety disorders, and substance use disorder[86,87].

The outcomes of psychiatric complications during the COVID-19 pandemic are complex for pregnant women since mental health problems are associated with adverse outcomes, including suicidal ideations and an unstable mother-infant bond[88]. Perinatal depression is also related to fetal complications, including fetal growth restriction and increased odds of premature delivery[89]. Maternal complications of depression are also associated with preeclampsia and gestational diabetes[77].

For many pregnant psychiatric patients, telehealth proves to be the most convenient way to obtain care. Due to governmental restrictions to halt the spread of COVID-19, many pregnant women cannot attend appointments in person. For socioeconomically disadvantaged women, telehealth can further the disparity of favoring those populations with resources to access technology *vs* those without, thus causing a gap in digital literacy[90]. This socioeconomic and educational disparity becomes apparent in developing countries where the prevalence of depression can reach around 15.6% during pregnancy and 19.8% after childbirth[91]. In Turkey, a recent online survey revealed that years of education and knowledge of COVID-19 protected against worsening of depression in pregnant women[77].

Another challenge complicating the mental health of pregnant women is dealing with the surge of domestic violence. For some pregnant women, more time at home may mean more time spent with an abusive partner[6]. According to the United Nations, domestic violence rates against women are increasing worldwide during the pandemic[92]. This increased rate is indicated by the number of calls received by emergency support lines in China, Italy, France, Brazil, and Spain during their lockdowns[85].

DISPARITIES IN MATURE ADULTS

Psychiatric patients who are mature adults are particularly vulnerable to COVID-19 because of a susceptibility to disease precipitated by a normal age-related decline in the immune system and comorbid conditions[8,93]. Comorbid conditions such as associated polypharmacy, hypertension, diabetes mellitus, chronic renal failure, and chronic obstructive pulmonary disease can contribute to an increased vulnerability to illness with poor health outcomes in this population[8,93,94]. Early identification of COVID-19 is key to mitigating illness in mature adults but can be challenging due to physical health factors.

Unique challenges are encountered specifically in mature adults with major neurocognitive disorder due to an atypical presentation of symptoms, such as low fevers, increased confusion, increased agitation, and sudden mood changes[95]. Upon the onset of the COVID-19 outbreak in China, the first psychiatric patient identified with the viral illness was a man hospitalized with a major neurocognitive disorder who supposedly ate outside food brought by family members and unknowingly infected others[8]. Masking protocols and appropriate handwashing can prove challenging to implement in the cognitively impaired within hospitals and long-term care facilities[8,96]. Mature adults with severe neurocognitive deficits may wander off, causing problems in implementing social distancing[96].

Another health inequity posited to affect mature adults more than other populations is self-isolation. Most of the daily social activities and contacts of many mature adults occur outside their homes[97]. In Canada, as the pandemic spread, leading to the cancellation of multiple community-based day programs for seniors[98]. During the early stages of the pandemic in China, self-isolation became a struggle, especially with mature adults without children or support, increasing the propensity to depressive symptoms[99]. Loneliness may also result from self-isolation. In Turkey, the pandemic has led to increased demand for home health aides to assist and accompany the elderly[94]. In the Caribbean, including Cuba, Puerto Rico, and the Dominican Republic, many mature adults with neurocognitive disorders live with extended family who can be of comfort and assistance[100]. Although social and physical distancing proves to be a difficult mitigating strategy, finding ways to connect and belong can help overcome the perceived loneliness of isolation.

Many mature patients also struggle with technology due to being unfamiliar with electronic devices, have difficulty navigating the internet or using platforms like those intended for telehealth appointments. There is a higher rate of illiteracy among the geriatric psychiatric population in the Middle East and North African countries[5]. Cognitive decline and lower education can add to the slow adaptation of technology and internet use in mature adults[94,101]. It is important to note that those mature adults who have higher education and seek social connectedness tend to adapt more rapidly to technology to overcome isolation[101]. For some mature adults who are marginalized, frequent phone calls and telephone calls from peer supports can help mitigate self-isolation[97].

DISPARITIES BETWEEN URBAN AND RURAL ENVIRONMENTS

Around 22% of Africa's population could become infected with COVID-19, a continent with a propensity to collective trauma due to the after-effects of the Ebola epidemic[101-103]. From 2014 to 2016, the Ebola virus outbreak caused psychosocial stressors such as discrimination, stigma, anxiety, and depression in Sub-Saharan communities[102]. In a cross-sectional study in Sierra Leone, knowing someone quarantined increased anxiety and depression, while PTSD was evident in 76% of Ebola virus survivors[104]. In many villages, healers and cultural treatment traditions were invalidated in preference for Westernized methods and treatment[105]. The government banned gatherings, and fear about the virus increased, causing heightened distress[105]. Due to overwhelming fears, many of the usual prevention methods of infectious spread were not practical during the Ebola epidemic[102,105]. Prevention methods to limit the spread of the Ebola virus were found to be poorly effective in those individuals with depression and trauma symptoms due to poor insight and impaired cognition[106]. Although it is unknown if the same prevention pattern with COVID-19 will result in individuals with depression, it is anticipated that such a similar pattern could occur since it has already been observed with other infectious diseases such as in the spread of HIV[106].

The inequity between urban and rural environments in mental health care becomes

evident in the villages' communal life in Africa. In these communities, there is a reliance on family members to provide for each other economically and to provide support to relatives with psychiatric symptoms[102]. The pandemic has led to income losses as many villagers can no longer sell farming goods or artisan items in urban centers[107]. Food security is an issue for many Africans during the pandemic due to economic availability[107]. Due to the governmental lockdown restrictions, the rural villagers can be further stressed, potentially increasing depression and anxiety[102]. When Africans display psychiatric symptoms, communal methods are usually exhausted first before sharing their symptoms directly to health care providers[102,105]. Plans to provide trauma-informed care by community health workers are primordial for the survivors of COVID-19 to prevent further re-traumatization due to discrimination, which was an issue with the Ebola virus[103]. Also, the ease of telehealth services is generally limited in rural environments compared to urban centers due to the availability of internet and poor signal reception[102].

The urban environment mental health disparity, which becomes apparent in densely populated cities, might be related to mitochondrial stress. Toxic metal pollutants in high dense areas can cause mitochondrial stress, increasing the vulnerability in psychiatric patients who already have mitochondrial dysfunction due to psychiatric illness, namely schizophrenia, bipolar disorder, and major depressive disorder, and who become infected and develop COVID-19 illness[17,108]. In Kuwait, a multi-ethnic country, South East Asians mostly live in highly populated dense areas where overcrowding and pollutants lead to higher exposure to COVID-19 illness[2]. This higher exposure can increase transmission of COVID-19, possibly leading to worsened mental health outcomes due to the potentiating effects of mitochondrial stress. A similar pattern occurs in Israel in which the Orthodox Jewish community populated in high dense cities contributes to an increased rate of transmission through religious rituals and gatherings[109].

LIMITATIONS

The minireview is limited mainly to observational studies due to the emergency state of the COVID-19 pandemic (Table 1). Articles in English and articles translated in English were reviewed, restricting the scope of the search. A lack of substantiated research in global health disparities, especially in ethnic minority groups, was appreciated in countries like Japan and South Korea. Although significant, other disparities involving prisoners, homeless persons, and persons with low educational attainment with psychiatric diagnoses during the COVID-19 pandemic were not addressed due to the narrow body of research.

It is essential to consider the short span since the pandemic's outbreak since the sequelae of COVID-19 are currently being studied in psychiatric and non-psychiatric patients[110,111]. The sequelae of COVID-19 may affect individuals with and without a history of psychiatric illness: A recent retrospective study showed that COVID-19 is associated with a higher incidence of a first psychiatric diagnosis following 14 to 90 days from exposure in non-psychiatric patients[110]. It is imperative to examine the impact of the COVID-19 pandemic on vulnerable populations without psychiatric illness. There is also a need to evaluate the impact on health care workers who face daily traumatic psychological stressors due to their job occupation and high exposure. Health care workers are confronted by an increased rate of mortality and increased health care demands[112].

CONCLUSION

The narrative minireview yielded evidence for worsened global mental health outcomes among vulnerable psychiatric patients during the COVID-19 pandemic. Psychiatric patients among vulnerable populations appear to be at higher risk for depression, anxiety, and posttraumatic stress symptoms. Among these vulnerable groups, collective trauma impacts marginalized individuals and communities. Expanding access to internet services and technical assistance in underserved areas can provide more effective delivery of psychiatric services through telehealth to vulnerable populations. Peer community supports for psychiatric patients can reduce social isolation. Programs promoting internet literacy for mature adults can support connectedness with family and relatives during prolonged periods of isolation. Providing programs that include psychiatric services with prenatal care can

potentially improve mental health outcomes in pregnant women. These findings suggest a need for greater implementation of programs that enhance communal resilience, decrease discrimination, and help overcome systemic barriers of care.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 April 19; 11(4): 109-123

DOI: 10.5498/wjp.v11.i4.109

ISSN 2220-3206 (online)

MINIREVIEWS

Use of technology and social media in dementia care: Current and future directions

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Author contributions: Shu S and Woo BKP both performed the collection of data and contributed to the manuscript drafting.

Conflict-of-interest statement: The authors declare that they have no conflict of interest regarding the content of this manuscript.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United States

Peer-review report's scientific

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Abstract

As the population across the globe continues to dramatically increase, the prevalence of cognitive impairment and dementia will inevitably increase as well, placing increasing burden on families and health care systems. Technological advancements over the past decade provide potential benefit in not only relieving caregiver burden of caring for a loved one with dementia, but also enables individuals with dementia to age in place. Technological devices have served to improve functioning, tracking and mobility. Similarly, smartphones, tablets and the ubiquitous world wide web have facilitated the dissemination of health information to previously hard to reach populations largely through use of various social media platforms. In this review, we discuss the current and future uses of technology *via* devices and social media to promote healthy aging in individuals with dementia, and also limitations and challenges to consider in the future.

Key Words: Dementia; Technology; Gerotechnology; Social media; Geriatrics; Wearable technology; Health promotion; Home health; Monitoring

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Core Tip: Technological advancements have the potential to re-define successful aging at home for individuals with dementia, bestowing sustained autonomy and independence, and also providing relief for families and caregivers. As gerotechnology continues to develop and is integrated into everyday life, research also continues to study how best to optimize usage and address older adults' preferences and concerns.

quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 5, 2021
Peer-review started: January 5, 2021
First decision: January 27, 2021
Revised: February 17, 2021
Accepted: March 18, 2021
Article in press: March 18, 2021
Published online: April 19, 2021

P-Reviewer: Zhang S
S-Editor: Gao CC
L-Editor: A
P-Editor: Li JH

Aims of this review are to examine and summarize current literature and technologies available and forthcoming that aid in diagnosis and successful aging in place, as well as challenges to be overcome.

Citation: Shu S, Woo BK. Use of technology and social media in dementia care: Current and future directions. *World J Psychiatr* 2021; 11(4): 109-123
URL: https://www.wjgnet.com/2220-3206/full/v11/i4/109.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i4.109

INTRODUCTION

With a rapidly aging population comes the rise in older adults living with chronic conditions. Of these, dementia has become one of the leading causes of disability and dependency worldwide[1]. Dementia is an umbrella term of symptoms that progress over time in which there is a gradual deterioration in cognitive and functional impairment and altered behavior. The etiology of dementia is myriad, with most common being Alzheimer's, and closely followed by vascular, Lewy body, frontotemporal, and mixed dementias. With unique pathologies and causative insults, each has its unique treatment to address the underlying cause. However, no cure currently exists for these dementias at large, nor treatment to alter its progressive course. Eventually unable to live independently, individuals with dementia require increasing levels of assistance and care. Therefore, goals for dementia care are focused on early diagnosis in order to optimize management in terms of physical health, cognition, activity and well-being.

Dementia care both in and outside of the hospital setting can prove challenging and complex. In addition to affecting individual quality of life, tremendous burden is placed on health care systems and families. One solution is to encourage and create a system for home-based dementia care. In 2015, a national consensus panel convened to address the burden of dementia and family caregiving[2]. Recommendations were made to shift the focus of future long-term care models to home based dementia care. Moreover, the majority of older adults prefer to stay in their homes for as long as possible than enter a nursing home when they require higher level care[3]. Technology, therefore, has the capacity to transform the course of dementia care, particularly at home.

Many technologies exist that have potential to support people with dementia and their caregivers through all stages[4]. Integration of existing and future technology presents an important opportunity for ameliorating the burden on individuals, families, and the health care system. A term coined "Gerotechnology" embodies this new interdisciplinary field of designing technology and an environment to promote independent living autonomy of older persons while strengthening the support of their networks[5]. Understanding and acceptance of use of technology in older adults are also key in the enduring adoption into everyday life. A recent study has established a 14-item questionnaire that can help assess older adults' acceptance of technology and effective usage[6].

In this review we address technology and social media targeted at health monitoring, proliferating dementia education and promoting psychosocial wellbeing of those with dementia. We summarize existing and in progress technologies that facilitate successful aging in place. Finally, we discuss limitations and challenges of implementing and integrating these technologies in the increasing population living with dementia.

TECHNOLOGY AS AN AID IN DIAGNOSIS

Research in Alzheimer's disease has grown exponentially over the past few decades[7]. Currently diagnosis of dementia is and remains primarily based on clinical history and presentation of the patient, with cognitive and functional testing. For Alzheimer's dementia, only post-mortem neuropathology is able to formally confirm a diagnosis. However, the advent of advanced medical imaging technologies and fluid biomarkers provide insight in the pathogenesis. As research advances, it is becoming clear that at

some point in the progression of dementia, lost neural networks cannot be regrown and excessive neurodegeneration cannot be reversed. Instead focus is shifting to slowing down early stages of progression and moreover, prevention: By reduction of overall improvement of health and wellbeing, chronic inflammation and oxidative stress[8].

Changes in how individuals use technology has been identified as an early indicator of emerging cognitive impairment. Seelye *et al*[9] designed a proof of concept study using continuous driving monitoring with unobtrusive sensors to identify and monitor subtle changes in driving patterns that may signal mild cognitive impairment (MCI). This study introduces a novel method in early detection and monitoring of functional changes in individuals with developing MCI.

Kamin and Lang[10] conducted a two-year longitudinal study looking at internet use and cognitive function in late adulthood. Looking at 29576 participants between 50 and 100 years of age, this study indicated that Internet use positively affects cognitive function in late life[11]. Similarly, Austin *et al*[12] conducted a longitudinal study in which a cohort of 113 older adult computer users were followed over a mean of 36 mo. They found that between participants with MCI and those who were intact, there was a significant decrease in the number of days with use, mean daily usage and increase in day-to-day use variability. Other studies suggest that even changes in the terms people search over the internet may be a measure of language and cognitive function in older adults[9].

Interestingly, Ihle *et al*[13] revealed in a six-year longitudinal study, the gender differences in the relationship between Internet use and cognitive decline, showing that more frequent Internet use predicted smaller subsequent cognitive decline only in men, but not in women. Together, these studies suggest the usefulness in incorporation of technology use in assessments for instrumental activities of daily living. They emphasize the potential that monitoring computer and technology use in diagnosing MCI and the progression of dementia over time, warranting further research in this area.

SMART HOMES: VOICE-ACTIVATED SMART SPEAKERS

The idea of "smart homes" is not novel. Smart homes are essentially the equipment of homes with sensors and various technology that facilitate the monitoring of inhabitants to improve quality of life and promote physical independence and reduce caregiver burden[14]. Services provided are far reaching from home automation of appliances, temperature and lighting systems, to remote monitoring capability of residents' wellbeing and safety (Table 1). With increasing prevalence and usage of smart home devices, older adults can potentially live independently and safely at home for longer, reducing or prolonging the need for caregivers both informally or formally[15].

Amazon currently has a line of Alexa-enabled home devices such as Echo, Echo Dot, and Echo Show. In addition to Amazon, there are various voice-activated smart speakers that also share similar functions[16]. Compatible smart home devices allow users to control lights and switches, set thermostats, view security cameras, thereby automating and simplifying everyday routines[17]. The Alexa mobile app includes a feature called 'Guard' that sends mobile alerts if an Echo device detects the sound of a smoke alarm or breaking glass. There is even a 'Hunches' feature that can help remind users to turn off a light or lock a door if Alexa has a 'hunch' that it was forgotten. More recently, Amazon recently launched a new feature called 'Care Hub' that allows consumers with an Alexa voice assistant to link their account to an aging relative's Alexa account[18]. This free feature includes activity feeds of smart home interactions, customized alerts for example if no activity is detected for a prolonged period of time, emergency contact notification capability, and quick access features allowing Alexa calling or 'Drop In'.

Several study protocols have been published as potential at home interventions to support caregivers of individuals with dementia[19,20]. The UP-TECH project proposed by Chiatti *et al*[19] was a 12 mo randomized controlled trial based in Italy with the purpose to reduce care burden of family caregivers and maintain Alzheimer's dementia patients at home. Technologies given included various housing adaptations such as sensors that detect falls, gas and water leak, and automatic lights. Outcomes measured were amount of caregiver burden and the number of days spent at home away from hospitalization or institutionalization. Other analyses measured were health economics, cost-effectiveness stratified by training time, social, costs of

Table 1 Summary of smart home and sensor technology

Technology	Functions	Originally developed for	Ref.
Alexa-enabled home devices, and Alexa Care Hub	Voice-activated smart speakers, connectable smart home devices, remote smart home monitoring	General use, older adults	Chung and Woo[16], and Amazon[17,18]
Tile	Locate misplaced items	General use	Tile[23]
Water-leak sensor	Smart water shutoff, mobile alerts	General use	D-Link[34], and Moen[35]
Google Nest Protect	Smoke and carbon monoxide alarm, 'pathlight' feature	General use	Google Store[38]
iGuard Stove	Smart stove shut-off valve, remote control and monitoring, emergency shut-off	Older adults	GoDaddy[39]
Automatic pill dispensers	Integrated alarms and reminders, multiple medication management, remote monitoring, adherence tracking	Older adults	Vervloet *et al*[42], Boland *et al*[43], Paterson *et al*[44], Hoffmann *et al*[45], Faisal *et al*[46], Ahmad *et al*[47], and Patel *et al*[48]

technologies and consumables for the interventions and health-related costs. In 2019, Socci *et al*[21] published the results showing high user satisfaction. Implementation and findings of this project are intended to support health care and social service professionals and policy-makers in the creation of future programs to address needs of Alzheimer's dementia patients and their care givers.

A similar study protocol based in Sweden, Malmgren Fänge *et al*[20] proposed a large randomized controlled trial called TECH@HOME. Aims were to recruit community-dwelling people with dementia and their primary informal caregivers and study the effects of technology on caregiver burden. Split into intervention and control groups, each intervention group would receive an information and communication technology kit including home-leaving sensors, smoke and water leak sensors, bed sensors, and automatic lights to monitor individual behavior. Home visits throughout the study period would measure primary outcomes of resource utilization, as well as secondary outcomes such as quality of life for both caregiver and person with dementia, caregiver anxiety and burden, and cost-effectiveness. Empirical data highlighted persons with dementia and their family members felt safe with the technology installed at home and felt that the technology was useful[22]. Ultimately sensor-based technology has the potential to be a support in ensuring a safer home environment for people living with dementia.

Results of these studies have the potential to inform policy makers and influence caregivers and families alike on the current state of technology. Implementation of similar study designs across the world are imperative in order to assess and inform of the current status of technology in alleviation of caregiver burden associated with dementia care and prolonging the independence of individuals with dementia in order to remain at home for as long as possible.

SENSORS AND SAFETY

Locator devices

Misplacing items is one of the most common symptoms of dementia, and as it can also be a common symptom of normal aging, persons living with dementia may be unable to find items again. Products such as 'Tile' are Bluetooth-enabled devices that can help locate misplaced items through activation of an audible alarm or last known position found on the mobile app[23]. From a simple tag on a keychain, card to slip into a wallet or laptop, or sticker for the remote control, products are designed to fit and locate the most common lost or misplaced items. Features include location history and also 'Tile Community' to use other individuals using running mobile Tile applications to help locate lost items when in Bluetooth range.

Falls, wandering, nighttime ambulation, security

Dementia-related wandering is present in up to sixty percent of community-dwelling people with dementia, and can be dangerous — even life-threatening — for patients and stressful for families and caregivers[24]. Modeled after the Amber Alert system for missing children, the 'Silver Alert System' was created in 2006 to provide a public alert

system about missing and vulnerable older adults[25]. Furthermore numerous technologies have been developed over the years to ease family and caregiver burden, locate missing persons and facilitate their return[26-28]. Providing a safe environment at home is important to continue to live independently and can be done by monitoring movements and alert carers or loved ones to potential breaches of safe boundaries. It is estimated that 30% of older adults fall at least once a year. Fall-related fractures can cause disability and even lead to premature death. The frequency of falls increases with age, as a result of physical, functional and cognitive impairment. Increasing technology-based interventions have been implemented for fall detection and alert[29].

There are a number of floor alarm mats by different companies. Floor pressure mats are good for fall-alarms when placed beside a bed or chair. Alternately, they can be placed at any doorway, such as an exit or the kitchen, to alert caregivers when their loved-one is on the move. Alerts can be in form of audible alarms or sent to connected smart devices. The doorway anti-wander safety beam can be placed alongside any doorway and send alarm sounds when the beam is crossed.

More innovative technologies include motion sensors embedded into socks and in floor tiles. Other floor pressure mats can be programmed to play recorded messages, for example a reminder to turn off the gas when walking out of the kitchen. There have been innovations such as the global positioning system (GPS) shoe, marketing itself as a way to locate individuals with Alzheimer's disease who have wandered away from home or their care facility. While they work with astonishing accuracy, and can be integrated with mobile application or professional call centers, there are also limitations and ethical considerations which will be discussed later[30-32].

Smart lighting technology also be placed in dark hallways and entryways to automatically turn on with motion sensor or *via* voice activation. Smart contact sensors can be multi-function. It can act as a whole home security system with alerts for open doors and windows, even refrigerator doors to indicate how often an individual has accessed comestibles. Options to self-monitor through mobile application or smart home system or professional monitoring with subscription are available. Combined, these technologies are promising to prevent or call to attention falls and wandering outside of the home and promote safer nighttime ambulation.

Water leaks

About one in fifty US homes file insurance claims annually due to water damage, which amounted to $13 billion in insurance payout for water damage[33]. These figures can easily be alleviated with technology to alert individuals of water leaks the instant they are detected. Smart water-leak sensor technology can be placed near areas of most likely leaks, such as the water heater, bathtub, sink, or toilet. Studies like the TECH@HOME study[20] have incorporated water leak sensor technology in home monitoring kits when studying technological interventions for individuals living with dementia. Currently there are many water leak detectors on the market, mostly embedded with smart technology that can be integrated into smart home systems[34,35]. Smart water shutoff can automatically turn off water supply in an emergency. Others offer wireless sensors that send alerts through mobile app in addition to triggering audible alarms or lights.

Fire safety

In 2004, the U.S. Fire Administration launched an intensive public fire education campaign for elderly Americans, and in 2006, published a report evaluating the fire situation and risks for this particular population[36]. Older adults are 2.5 times more likely to die in fires than the overall population. Common fire causes resulting in injury among the older population are cooking, open flames, smoking and heating. Decreased sensory abilities like smell, touch, vision and hearing that come with aging, and compromised cognition with progressive dementia can all contribute to impairing ability to prevent or respond to fires. Hearing impairment is the second most commonly reported in older adults in the United States[37]. The inability to hear warning sounds of fire or a smoke alarm creates significant fire risk. This decrease in reaction time and awareness places older adults at higher risk of fire, fire injury and fatality. Attention therefore needs to be placed on making the necessary home improvements to reduce fire risk. Unfortunately, many of these are overlooked or postponed because of cost or lack of knowledge or attention.

Technologies such as 'Google Nest Protect' acts as a smoke and carbon monoxide alarm that alerts by voice and siren and is capable of sending smartphone alerts to up to six contacts[38]. Also integrated into its device is a 'Pathlight' feature, a motion-activated night light.

Stove-top technologies such as the smart stove shut-off valve allows for remote

control and monitoring of stove settings and emergency shut-off system. Technologies such as the 'iGuard Stove' boast automatic shut off after 5 min of no presence in the kitchen, day and night-time activity monitor, night lock and caregiver lock modes, and alerts sent to mobile application[39].

MEDICATION AIDS

Unintentional medication nonadherence is increasingly prevalent with an aging population, particularly in older adults with compromised functional and cognitive capabilities, multiple chronic health conditions on complex medication regimens[40,41]. Current strategies to address medication management adherence include pillboxes, visual or audio reminders or alarms, and automatic pill dispensers[42-44]. Of the multiple automated pill dispensers currently on the market, these products have many features including integrated alarms and reminders and ability to manage multiple medications. Dispensers are connectable to smartphone *via* application and can notify users and allow remote monitoring. Applications can track adherence and also notify when certain medications are running low. Some devices are able to store and dispense up to 90-d supply of up to 10 different medications. Unfortunately, this creates limitations for individuals taking more than the maximum allowed medications each machine is able to manage, requiring need to decide which scheduled medications are most important to track, or allow another application to manage medications outside of the device. Other limitations are the type of medication: Some dispensers will not work with half pills, gummies, powdery, sticky or dissolvable pills.

Hoffmann *et al*[45] studied whether automated home medication dispensers could help solve unintentional medication nonadherence. Using a 6-mo prospective study in 21 patient-caregiver dyads, they found that mean adherence increased from 49.0% at baseline to 96.8% ($P < 0.001$).

Faisal *et al*[46] and Ahmad *et al*[47] examined user experience with electronic medication adherence products. Both studies have demonstrated that these products have potential to promote independent medication management in older adults. Choice of products are based on product features, facility of use, portability, and affordability. Unfortunately, many medication dispensing systems have a monthly managing free in addition to the upfront cost of the machine itself, therefore use of such technology can be limited by cost.

Patel *et al*[48] used a prospective, mixed methods study to test the usability and workload of twenty-one electronic medication adherence products. Each of 39 participants tested five products, one at a time and usability and workload were compared in the different products. This study highlights the importance of comparing products within target populations in order to guide clinicians, caregivers, and users themselves in choosing the most optimal product for their particular needs.

Alternative to automated medication dispensers, mobile applications can be a useful standalone assistive technology to ensure medication adherence. Chew *et al*[49] looked at the usability and utility of a mobile application called 'Med Assist' to improve medication adherence. To date, there are several medication adherence applications, but few studies have been conducted among their target population. Through two rounds of 'think aloud' interview and a retrospective interview at the end of using the application for a week, results showed positive feedback from participants regarding usability and reliability. Ease of navigating through the application, multiple user support capability and medication refill reminders were all positive aspects that participants found that suggest the efficacy of this and similar mobile health applications to improve medication adherence.

WEARABLE TECHNOLOGY

Wearable technology, particularly wrist-worn devices, can impact key aspects of dementia care management by providing insight into specific factors that are key determinants of health and wellbeing[50,51]. Devices are able to provide quantified information on sleep and physical activity, with more advanced technology having embedded heart rate monitor, arrhythmia and fall detection, and GPS. These objective measurements have potential to guide physicians in clinical decisions by having a tool that simplifies and facilitates data collection in a manner previously impossible. Available devices offer easily accessible and user-friendly interface. Contrary to life-

alert or medical alert buttons that have stigma of making wearers 'feel old', wrist-worn devices offer more sleek and discreet designs that can appeal to older adults. With so many available functions, these devices can aid in the care and management of older adults with dementia.

Megges *et al*[52] studied the user experience and clinical effectiveness of two similar wearable GPS watch devices. Over a period of 4 wk, measures such as usability, design features, and overall product satisfaction were taken by patients and caregivers. Feedback and findings included preference for fewer buttons, clear display and font, and ample battery life. Future comparison of GPS devices, particularly watches, are of interest in order to study how likely they are to be adopted.

A recent case study described how use of a wrist-worn device was able to aid physicians in diagnosis, treatment decision making and prognostic monitoring of treatment of an older adult's late-life depressive symptoms[53]. The patient was encouraged by the ability to track and visualize his own activity and sleep and reported positive reinforcement for remaining engaged in exercise as it noticeably improved his depression.

As many older adults already own wrist-worn devices demonstrated by the plethora of commercial wearable devices available by companies such as Apple[54], Fitbit[55], Garmin[56], and Huawei[57], it is no wonder that these devices are becoming the focus of future research that can not only support older persons with dementia, but also revolutionize the way we collect 'big data' for studying populations in aggregate[58].

Amazon most recently launched 'Halo', a wearable band and health and wellness tracker detecting body fat composition, sleep and activity tracking, and most uniquely, tone of voice analysis[59]. Voice qualities such as pitch, intensity, rhythm, tempo analyze and report emotion states of 'hopeful, elated, hesitant, bored, worried, confused, affectionate' for users to become more aware of their mood, interactions and relations throughout the day. Goals of this device are focused more on providing means for lifestyle changes including at-home workouts, guided meditations and sleep sounds.

SOCIAL MEDIA

Today more than ever, people are turning to the internet for health information. Social media are a valuable tool to deliver health education to different populations. Different platforms are available on mobile devices that facilitate information acquisition and sharing and the use of these by people globally are on the rise.

Studies have shown that YouTube is effective in delivering dementia education to older adults[60,61]. Similarly, Twitter is a novel platform for Alzheimer-related dementia awareness[62]. Other studies explore how social media platforms such as WhatsApp are becoming strong means of disseminating health information[61,63]. Further efforts in studying and optimizing how we use social media to recruit, disseminate and share health information can prove invaluable in reducing the gap in health literacy and ensure healthy aging and promotion of healthy outcomes.

It is important to consider the perceived usefulness of technology in the older adult population. Best *et al*[64] conducted a study showing a positive relationship in the perception of usefulness of computers in providing health-supporting technologies. Furthermore, Berkowsky *et al*[65] looked at different factors that predict technology adoption among older adults. With fifty-two older adults participating, they found that self-assessed abilities and computer-internet skills were predictive of individual willingness to adopt technologies. However most robust predictors were perceived value and impact on the quality of life, and confidence in ability to learn the technology. Therefore, in developing new technologies, consideration must be made in balancing functionality with complexity in order to maximize potential of technology adoption among the aging generation.

ARTIFICIAL INTELLIGENCE

The use of artificial intelligence, or robotic technology, has been explored over the years. Robots have been made to either be physically assistive (performing physical tasks), or socially assistive (providing social and psychological support).

Therapeutic robots

With progression of dementia comes increased behavioral and psychological symptoms of dementia that can be difficult for family and caretakers to manage. Non-pharmacologic interventions are sought after before turning to psychotropic medications. Therefore, therapeutic robots in form of animals may be promising forms of therapy that are also facility friendly as some do not allow animals to visit and are furthermore not limited by animal allergies.

One of the earliest examples of such social robot is PARO (comPAnion RObot), a baby harp seal robot developed in Japan as pet therapy for patients with dementia[66]. PARO is powered by artificial intelligence to respond to the user and the environment, can move its tail and fliggers, open and close its eyes, and make sounds similar to a real baby harp seal. Now an FDA approved biofeedback device, PARO's benefits, including psychosocial, have been widely studied over the past ten years all over the world. Studies have shown PARO to be a viable alternative with therapeutic benefit in managing symptoms of anxiety, depression, and chronic pain in patients with dementia, improving sleep, social interaction and overall quality of life[67-73]. Moyle *et al* [74] led one of the largest pilot studies of use of PARO at long-term care facilities in Australia. By using a cluster-randomized controlled trial, studying four-hundred participants with documented diagnosis of dementia across twenty-eight long-term care facilities across Australia, results revealed that participants with interaction with PARO (15-min sessions 3 times a week for 10 wk) were more verbally and visually engaged, and had improved mood states and agitation.

Ollie the baby otter was built by a team of undergraduate engineering students at Massachusetts Institute of Technology in 2013[75]. The prototype was created with the intention of being a therapy robot to help with anxiety and depression in patients with dementia, and more affordable than the Japanese robotic seal PARO. Similarly NeCoRo was designed as a robotic lap cat by a company called Omron in Japan and has also been the subject of research of robotherapy for older persons with dementia[76,77].

In December 2015, Hasbro released a line of companion pets called 'Joy for All' intended to provide stuffed animal therapy for individuals experiencing age-related memory loss. Now expanded into its own company: Ageless Innovation, the Joy for All line of robotic companion pets advertises therapeutic benefits such as decreasing anxiety and agitation, increased feelings of self-worth, improved mood and physical activity, and increased interaction with others[78]. Currently available are a golden retriever pup and a variety of cats all with positive testimonials from the older adult market.

The Hug by Laugh research project was development to support people with late stage dementia to amuse, comfort, engage, bring joy and improve overall wellbeing[79]. Hug is equipped with a beating heart and ability to play music that can be personalized to a favorite playlist.

Other technologies such as humanoid social robots are also being studied. One in particular called Kabochan was studied in 103 residents with dementia across seven long-term care facilities in Hong Kong. Assessed by randomized controlled trial over 32-wk, Ke *et al*[80] suggest that engaging with humanoid social robots may be promising in changing perceived ease of use of technology and that Kabochan was about to reduce short-term neuropsychiatric symptoms and caregiver distress[81].

The future of robotic product designs is promising in delivering social support, enhancing well-being and quality of life for individuals living with dementia (Table 2). As more robotic product designs are developed, socially interactive robots are being studied more and more, providing valuable insight into features and functions that these technologies can serve[82].

Assistive service robots

Service robots have the potential to assist older adults with dementia by helping to complete everyday tasks. Equipped with video chat capabilities, such robots are also able to support socially by reducing isolation. Services include reminders to complete activities of daily living such as brushing teeth, drinking water, dressing, and taking medications. Others are being developed with functional arms to reach for and bring items to the user. With the number of innovations, it becomes important firstly to study preferences and perspectives of users and whether technologies will be likely to be accepted and adopted into assisting with care of persons with dementia.

Korchut *et al*[83] worked to identify challenges for service robots in consideration of the requirements of older persons with cognitive impairments. Based on 264 surveys conducted in focus groups of medical staff, potential users and caregivers across

Table 2 Summary of therapeutic robots

Technology (company)	Form	Functions and intentions	Ref.
PARO	Baby harp seal	Managing psychosocial symptoms of anxiety, depression and social interaction	Hung *et al*[66], Petersen *et al*[67], Pu *et al*[68], Lane *et al*[69], Jøranson *et al*[70], Liang *et al*[71], Jøranson *et al*[72], Jøranson *et al*[73], and Moyle *et al*[74]
Ollie (Massachusetts Institute of Technology)	Baby otter	Relieve psychosocial symptoms of dementia	IEEE Spectrum[75]
NeCoRo (Omron)	Lap cat	Tactile and recognition sensors and feedback to engage individuals with dementia	Megadroid[76] and Libin and Libin[77]
Joy for All (Hasbro)	Golden retriever pup and cats	Providing social support for individuals experiencing age-related memory loss	Ageless Innovation[78]
Hug by Laugh	Humanoid	Amuse, comfort, engage, beating heart, personalized music playlist, bring joy to support people with late-stage dementia	Hug by Laugh[79]
Kabochan	Humanoid	Reduce neuropsychiatric symptoms and caregiver distress	Ke *et al*[80] and Chen *et al*[81]

Poland and Spain, priority function requirements of service robots were related to reacting in emergency situations and reminders about medication. Almost 60% of surveys indicated reminders about boiling water, turning off the gas and lights as priority. Similarly, Bedaf *et al*[84] surveyed the preferred characteristics of service robots across older adults, informal and professional caregivers across The Netherlands, France and the United Kingdom. Expectations involved customizability of service robots to match user needs and preferences, and also functioning and behavior with qualities similar to that of a human. Wang *et al*[85] further documented perspectives of older adults and their caregivers on using home assistive robots. They found that older adults were curious and open to the idea of using assistive robots, provided that there is clear perceived need and benefit.

In sum, service robots' ability to help older adults carry out daily activities may help to relieve caregiver strain and promote social relationships and cognitive support. However, balance needs to be maintained in order to uphold autonomy, privacy and dignity for the older adult.

DRIVERLESS VEHICLES

Driving is the predominant mode of transportation for older adults in the United States. However, driving with a compromised functional ability or lengthened reaction time, individuals with progressive dementia can eventually become a danger to themselves and others while on the road. Cessation of driving severely reduces ability to maintain previous social participation, and even disrupt a means to live including transportation to shopping and doctor appointments. Therefore, taking away a license to drive can severely prove a hindrance to living independently. Driving mobility may be composed of both either individual ability to drive or ability to obtain a ride or another means of transportation likely from a friend or caregiver. This added dependence can eventually create burden or strain on others. Automated vehicles are a rapidly developing technology with a spectrum of features from providing warnings and momentary assistance during full human operation, to transient assistance and support in steering or braking, to full automation.

In assessing awareness and openness in using automated vehicle technology, Oxley *et al*[86] found that despite low awareness of in-vehicle safety features among a sample of older adult active drivers, there was greater interest in purchasing vehicles with safety features when aware.

'Waymo' began as the Google self-driving car project in 2009 with the mission of facilitating safe transportation and access to mobility for those who may be unable to[87]. Similarly, self-driving cars by Tesla[88], General Motors[89], Toyota[90], Honda[91], and so many more reflect the rapid proliferation of this technology in the near future. 'Voyage', a start-up company based in California, is working to develop self-driving technology with the mission to provide transportation for millions of senior citizens living in retirement communities[92].

While still in early testing phases before phasing into the market, it is unclear how it

will be perceived and adopted by the public. But it is clear that there is a broad range of potential positive impacts of automated vehicle technology in the lives of older adults. Even more broadly it can help bridge disparities in social and environmental determinants associated with health[93].

CONCLUSION

With current trends towards 'aging in place', technology holds promise in helping to maintain autonomy of persons with dementia over time. When envisioning the future for older adults in the context of aging in place, technologies should be developed with goals of supporting both autonomy and independence in addition to safety[94]. While dementia is indeed a spectrum of symptoms with various etiology, and there is little to formally diagnose, for example Alzheimer's, until post-mortem, it is difficult to ascertain specific recommendations specific to each type of dementia. There is currently no neuropsychological assessment aimed at determining which technology or social media would be best suited for individuals with specific dementias. Rather, decision to adopt and implement technologies into everyday life is an individualized decision based on personal needs and goals. Creation of a formal standardized assessment to guide recommendations towards particular technology or social media is an area of future consideration and direction. Though there is indeed a limitation of specificity in utilization, with more scientific advancements in uncovering biomarkers for different dementia phenotypes, we foresee more specific recommendations to come in the future.

With the rise in use of technology, it also behooves us to consider ethical ramifications. Firstly, the existence of assistive technology has the intention of providing safety and assurance to help individuals be able to age in place. However, the mechanism of doing so introduces alternative methods of surveillance, thereby limiting privacy and restricting movement for persons who were once regarded independent. Wearable technology, home safety monitoring and location devices may be assumed as a breach of privacy even if the monitor is a close family member or friend. Be it covert or with full knowledge, or for an individual without capacity to make such decisions, the perceived loss of independence for the sake of maintaining a level of independence begs the question of how much privacy is permissible to be lost before crossing boundaries of invasion of privacy and autonomy. Such a balance of privacy *vs* utility needs to be addressed and taken into consideration when developing new technologies.

With respect to use of robotic technology, social robots' purpose is to enhance social interaction. The notion of person-to-person interaction is invaluable and can never really be replaced but critics may argue that technology, particularly use of robotic technology, undermines this entire concept. However humanoid, the use of robots in place of humans in order to partially relieve caregiver burden is a fine line to tread. A case can be made, however, for robotic pets to allay negative psychological characteristics inherent across various stages of dementia. It can be a practical alternative in environments with insufficient staffing resources, allergy limitations to real animals, safety concerns about pet behaviors or disruptive behaviors of individuals towards a real animal. Notwithstanding, the progressive loss of ability to socialize and increased behavioral symptoms are characteristic of late dementia, imploring the determination of when during the course of dementia would robotic technology, if ever, shall be deemed appropriate regardless of severity. Work needs to be done to evaluate to what extent is replacement of human interaction considered enhancement of social interaction instead of limiting and viewed as a devaluation of caring.

Practical challenges in widespread adoption of gerotechnology among older adults include financial limitations of cost of device, installation, and monitoring. Adoption of such promising technologies are thereby limited foremost by economic ability to finance, both personally and within scope of health insurance plans. This highlights a burgeoning facet that needs to be addressed in the scope of health economics. Efficient, cost-effective distribution of this increasingly valuable resource is necessary in order to most effectively alleviate healthcare burden of caring for individuals with dementia. In terms of prioritizing public health and management of health services, looking into maximizing the years of healthy life from use of these technologies can elucidate a clearer picture of the benefits to be expected. Critics may argue that the benefits are not worth the price tag that comes with equipping every older adult with technologies that enable aging in place. More quantitative evidence to measure effectiveness of these

technologies can be useful in deliberating health policy efforts, focusing on aid in funding and finance to make technologies more affordable and thereby more available to beneficiaries. Partnerships with companies to lower cost of manufacturing would help to ultimately lower cost for consumers. Currently, many if not all health insurances do not cover these technologies and individuals must pay out-of-pocket. Further work therefore needs to be done to highlight the potential of these technologies to alleviate healthcare burden in order to drive healthcare policy to aid in funding and finance to enable people with dementia and their care-givers access to these services. Work also needs to be done in educating the public, *via* ever present social media, to awareness and necessity of available technologies, and for assistance and support on how to use the technologies.

Furthermore, in developing these technologies, preferences and sustainability across all stages of aging and dementia need to be considered in order to deliver high-value, needs-based, dementia-centered care. Technology truly has the potential of creating a patient-centered care home that can ensure people living with dementia have a safe, healthy environment to live independently for as long as possible. As such an interdisciplinary field, gerotechnology presents a collective endeavor to equip older adults with the resources to successfully age in place.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 April 19; 11(4): 124-132

DOI: 10.5498/wjp.v11.i4.124

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Chronic serotonin syndrome: A retrospective study

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Author contributions: Prakash S was involved in the conceptualization of the project, data collection, statistical analysis, supervision of the project, and writing the original draft; Rathore C was involved in the analysis and interpretation of data and writing the original draft; Rana K was involved in the analysis and interpretation of data and revising the manuscript for intellectual content; Roychowdhury D was involved in data collection and revising the manuscript for intellectual content; Lodha D was involved in data collection and revising the manuscript for intellectual content; All authors approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Sumandeep Vidyapeeth Institutional Ethics committee, Piparia, Vadodara, India (SVIEC/ON/MEDI/RP/20116).

Informed consent statement: Written informed consent was taken from all patients to publish this observation.

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Abstract

BACKGROUND

Serotonin syndrome (SS) is an underdiagnosed drug-induced clinical syndrome resulting from the excess intrasynaptic concentration of serotonin. Very limited information is available about chronic SS.

AIM

To evaluate the epidemiological, clinical, and other aspects of the insidious onset SS.

METHODS

We retrospectively evaluated 14 consecutive adult patients (> 18 years) who had complaints for more than 6 wk at the time of consultation and met the Hunter criteria for SS.

RESULTS

The mean age was 41.1 years (range: 21-61 years), with a male preponderance (64%). Although tremors were observed in all patients, this was a presenting complaint in only 43% of patients. Generalized body pain, insomnia, and restlessness were common presenting features (50% each). Other common clinical features were stiffness of the limbs (43%), diaphoresis (43%), gait disturbances (36%), bowel disturbances (36%), dizziness (29%), sexual dysfunctions (21%), incoordination (14%), and fatigue (14%) The mean duration of symptoms before the diagnosis of SS was 13.5 ± 5.8 wk (range: 6-24 wk). Amitriptyline was the most common drug (n = 6, 43%), followed by tramadol (n = 5, 36%) and sodium valproate (n = 5, 36%). All patients received cyproheptadine, a 5-hydroxytryptamine2A antagonist, as treatment and noted an excellent response

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

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Manuscript source: Invited manuscript

Specialty type: Clinical neurology

Country/Territory of origin: India

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 14, 2020
Peer-review started: December 14, 2020
First decision: January 18, 2021
Revised: January 21, 2021
Accepted: March 9, 2021
Article in press: March 9, 2021
Published online: April 19, 2021

P-Reviewer: Plaza MA
S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Li JH

over the course of 4-14 d.

CONCLUSION

This study represents the largest study on chronic SS. We suggest that patients receiving serotonergic drugs should be physically examined for the presence of SS upon the development of new symptoms.

Key Words: Serotonin syndrome; Serotonin toxicity; Cyproheptadine; Serotonergic agents; Serotonin; Clonus

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Core Tip: Chronic serotonin syndrome (SS) is an evolving concept. It may present with nonspecific symptoms such as generalized body pain, stiffness/rigidity, insomnia, restlessness, and tiredness. As misdiagnosis is common for typical cases of SS, a high level of clinical suspicion is required to identify patients with a chronic variant. A detailed drug history and thorough physical examinations are needed to detect a case of SS. Diagnosis of even mild SS is important as inadvertent use of another serotonergic agent may worsen the clinical symptoms, and sometimes it can be fatal.

Citation: Prakash S, Rathore C, Rana K, Roychowdhury D, Lodha D. Chronic serotonin syndrome: A retrospective study. *World J Psychiatr* 2021; 11(4): 124-132
URL: https://www.wjgnet.com/2220-3206/full/v11/i4/124.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i4.124

INTRODUCTION

Serotonin syndrome (SS) is a drug-induced clinical phenomenon characterized by a triad of altered mental activity, neuromuscular hyperactivity, and autonomic disturbances. It occurs due to increased intrasynaptic concentration of 5-hydroxytryptamine (5-HT) or serotonin. Although SS is a potentially fatal condition, misdiagnosis for SS is common in clinical practice. Misdiagnosis is partly due to its protean manifestation and partly due to unfamiliarity about SS among physicians[1]. The incidence of SS is increasing worldwide due to the widespread use of various serotonergic agents. Several new concepts about SS have emerged in recent years that further complicate clinical issues associated with SS. In earlier years, SS was commonly reported in patients with psychiatric disorders, especially from toxicology centres. The identification of a variety of serotonergic agents in the past decades has expanded the clinical scenarios where SS can be noted. Cases of SS are being reported from non-toxicological departments and clinics, including surgical departments (perioperative settings), cardiac departments, headache clinics, gynaecological clinics, and paediatric clinics. Moreover, a few drugs with serotonergic properties are not marketed as serotonergic agents (such as dextromethorphan, fentanyl, linezolid, tramadol, and methylene blue). The clinical spectrum of SS has increased dramatically in recent times, and several atypical features have been noted in patients with SS[2]. The literature on SS is a bit biased for acute and severe cases, and there are only a few cases of SS that had insidious onset and prolonged course[3-5].

The onset of SS is typically described in the setting of recent administration of a proserotonergic agent. The administration of proserotonergic agent means starting a drug for the first time, increasing the dose, taking an overdose (accidental or suicidal), adding other serotonergic agents, and swapping of serotonergic agents. However, SS, including severe and fatal cases, may occur even with a stable dosage. In a review of 56 cases of fatal SS, seven patients (13%) were on a stable dosage, and there was no change in the dosage of the drugs in the recent past; and all of them had insidious onset SS[6].

The diagnosis of SS is typically made according to either the Hunter criteria or the Sternbach's criteria, and both the diagnostic criteria are primarily intended to detect acute and severe cases[7,8]. The Hunter serotonin toxicity criteria require the presence of one of the following clinical features in the presence of serotonergic agent use: (1)

Spontaneous clonus; (2) Inducible clonus/ocular clonus with diaphoresis or agitation or rigidity, with a temperature > 38.0 °C; and (3) Hyperreflexia and tremor[7]. A combination of tremor and hyperreflexia is generally noted with mild and insidious onset SS. To the best of our knowledge, no studies dedicated to insidious onset chronic SS have been conducted to date. Chronic SS is not defined in the literature. The term 'chronic' is often used when the course of the disease persists for more than 3 mo. However, in a few clinical conditions, the time limit for chronic conditions is less than 3 mo. The time limit for chronic myelitis and chronic osteomyelitis is 6 wk. Considering the seriousness of SS, we used 6 wk to define the time frame of chronic SS in this publication. Herein, to discover the different aspects of insidious onset chronic SS, we evaluated the data of the patients who met the Hunter criteria for SS and simultaneously had symptoms for more than 6 wk.

MATERIALS AND METHODS

This study was conducted as a retrospective chart review of all consecutive adult patients (≥ 18) who had 'presenting complaints' for more than 6 wk at the time of the first consultation and met the Hunter criteria for SS (Hunter criteria described above). The study included patients with a minimum of 6 wk of follow-up. The exclusion criteria included: (1) Age < 18 years; (2) A follow-up of less than 6 wk; and (3) Patients who did not give consent. Included patients were seen between February 2018 and July 2020 in the Neurology Outpatient Department of Smt. B.K. Shah Medical Institute and Research Center, Vadodara, India. Epidemiological, clinical, laboratory, management, and outcome data were collected from medical records. Our team has been working on SS for several years. Therefore, as a departmental policy, any patient fulfilling the Hunter criteria is routinely subjected to a detailed clinical history and physical examination. So, all the data were collected prospectively at the time of the first consultation. The Institutional Ethics Committee approved the study (SVIEC/ON/MEDI/RP/20116). The study was done according to the Helsinki Declaration guidelines. Written informed consent was taken from all patients to publish this observation. We used statistics with mean ± SD for continuous variables and frequencies and percentages for dichotomous variables. Anonymized data not reported here can be obtained from the corresponding author on rational demand by any qualified researcher.

RESULTS

We identified 19 patients who met the inclusion criteria. Five patients were excluded for the following reasons: Age less than 18 years (n = 1 patient), follow-up less than 6 wk (n = 2 patients), and those who did not give consent (n = 2 patients). As cases of chronic SS are not well described in the literature, we are providing details of three patients. The clinical characteristics of the other 11 cases are summarized in Table 1. Epidemiological, clinical, and other characteristics of all 14 cases are summarized in Table 2.

The median age at symptom onset was 44.1 years (range: 21-61 years), with a male preponderance (64%). All patients had tremors and hyperreflexia. A combination of tremors and hyperreflexia/inducible clonus sufficed the Hunter criteria. In addition, 11 patients (78%) also fulfilled the Sternbach's criteria of SS. Generalized body pain, insomnia, and restlessness were common presenting complaints (n = 7 patients, 50% each). Although tremor was observed in all patients, it was part of the presenting complaints in only six patients (43%). In other patients, tremors were detected only after neurological examinations. Other common symptoms included diaphoresis (n = 6 patients, 43%), gait problems (n = 5, 36%), bowel disturbances (n = 5, 36%), dizziness (n = 4, 29%), sexual dysfunctions (n = 3, 21%), incoordination (n = 2, 14%), and fatigue (n = 2 patients, 14%). Besides hyperreflexia (100%), clonus (n = 13 patients, 93%) and rigidity/spasticity (n = 11 patients, 79%) were two common physical signs. Tachycardia was reported in 9 (64%) patients. Fever was not reported in any patient. The mean duration of symptoms before getting the diagnosis of SS was 13.5 ± 5.8 wk (range: 6-24 wk). While 36% of patients were on a single serotonergic agent, about 64% of patients received two serotonergic agents. There was no history of an overdose of any serotonergic agent, and all patients were on stable doses of serotonergic agents for various periods. Amitriptyline was the most common agent causing SS (n = 6 patients, 43%), followed by tramadol and sodium valproate (n = 5 patients, 36% each). We

Table 1 Details of patients with chronic serotonin syndrome

Age/sex	Details of the clinical characteristics			Serotonergic agent and its details	Investigations	Treatment and follow up
	Presenting complaint	Other symptoms and signs	Duration of illness			
49, F	Generalized body pain, fatigue, restlessness, tremors	Dizziness, insomnia, tachycardia, rigidity, clonus	6-8 wk	Valproate for 2 yr for epilepsy, sertraline added 3 mo back for depression	CK- 566 U/L	Discontinued sertraline. Cyproheptadine (4 mg bid) was started. Marked improvement in 2 d. Complete response within 5 d. No recurrence in follow-up
57, M	Irritability, disturbed sleep, slowness in gait, disturbed bowel	Tremors, sexual dysfunctions, tachycardia, rigidity, clonus	3 mo	Tramadol and amitriptyline for paraesthesia for 1 yr	Normal	Discontinued drugs. Cyproheptadine (4 mg bid) was started. Response began within 48 h. Complete response within 7 d
32, F	Headache, generalized body pain, tremors	Intermittent diaphoresis, tachycardia, rigidity, clonus	2 mo	Valproate (500 mg bid) for 6 mo for epilepsy	CK- 1283 U/L	Marked improvement by cyproheptadine (4 mg tid). Valproate changed to levetiracetam. Follow- up was uneventful
46, F	Slowness in work and gait, bladder dysfunctions, dizziness, tremors	Dizziness, sexual dysfunctions, tachycardia, rigidity, clonus	3 mo	Amitriptyline and citalopram for 1 yr for bipolar disorder	Normal	Discontinued the offending drugs. Cyproheptadine (4 mg tid) for 3 wk. Response began in 48 h. Complete response within 10
58, M	Slowness in gait, pain and stiffness in the limbs and neck, tremors	Nystagmus, tachycardia, rigidity, clonus	10-12 wk	Tramadol, and fluoxetine for 4 mo for carpal tunnel syndrome	CK-879 U/L	Cyproheptadine (4 mg tid) for 2 wk. Response began in 2 d. Complete response within 5-7 d. No recurrence in follow-up
37, F	Tremors, irritability, fatigue, muscle pain, bowel disturbances	Tachycardia, hypertension, hypertonia, clonus	8-10 wk	Amitriptyline and valproate for chronic migraine for 6 mo	Normal	Started cyproheptadine (4 mg bid). Complete response within 4-6 d. Cyproheptadine was continued as an anti-migraine drug
31, M	Gait problems, stiff legs, bowel disturbances	Tremors, spasticity, clonus, diaphoresis	9-10 wk	Paroxetine (40 mg/d) for 6 mo for depression	CK-1279 U/L	Discontinued paroxetine. Cyproheptadine (6 mg tid) for 3 wk
47, M	Insomnia, dizziness, restlessness, bowel disturbance, episodic sweating	Tremor tachycardia, rigidity, clonus, hyperreflexia	3-4 mo	Sertraline and valproate for mood disorder for 9 mo	CK-634 U/L	Discontinued both drugs. Cyproheptadine (4 mg bid) for 4 wk
42, F	Generalized body pain, stiff body, constipation	Tremors, nystagmus, rigidity, stiff neck, hyperreflexia	8-10 wk	Tramadol and amitriptyline for 3 mo for pain after radius fracture	CK-1134 U/L	Started cyproheptadine (4 mg tid). Marked response in 7 d. Cyproheptadine was continued for 6 wk
54, M	Dystonic tremor, incoordination, stiffness in legs, episodic sweating	Tremors, nystagmus, rigidity, clonus, hyperreflexia	6-8 wk	Amitriptyline and tramadol for 3 mo for cervical spondylosis	Normal	Stopped both drugs. Started cyproheptadine (4 mg tid). Complete response in 7 d. Cyproheptadine was continued for 6 wk
61, M	Tremors, stiffness, incoordination, sexual dysfunction, insomnia	Nystagmus, rigidity, clonus, hypertension	4-5 mo	Addicted to tramadol for 2 yr for neuropathic pain	Normal	Marked improvement with cyproheptadine (4 mg tid). The patient did not stop tramadol and he continued cyproheptadine

F: Female; M: Male.

found two cases each with paroxetine and sertraline. There was 1 case each with citalopram and fluoxetine. Creatine kinase levels were raised in 6 patients (43%). Cyproheptadine, a 5HT2A antagonist, is the main drug used in cases of SS, and all patients received cyproheptadine. All patients showed a complete or almost complete response to cyproheptadine over 4–14 d.

Table 2 Epidemiological profiles and clinical features of 14 patients with chronic serotonin syndrome

Parameters	*n* (%)
Age in yr, mean ± SD	44.1 ± 11.6
Sex, M:F	9:5 (1.8:1)
Duration of illness in wk	13.5 ± 5.8
Clinical characteristics	
Tremor	14 (100)
Hyperreflexia	14 (100)
Clonus	13 (93)
Spasticity-rigidity	11 (79)
Tachycardia	9 (64)
Generalized pain	7 (50)
Insomnia	7 (50)
Irritability-restlessness	7 (50)
Stiffness	6 (43)
Diaphoresis	6 (43)
Gait disturbances	5 (36)
Bowel disturbances	5 (36)
Dizziness	4 (29)
Sexual dysfunctions	3 (21)
Nystagmus	3 (21)
Hypertension	2 (14)
Incoordination	2 (14)
Fatigue	2 (14)
Fulfilments of SS criteria	
Hunter criteria	14 (100)
Sternbach's criteria	11 (78)
Serotonergic agents implicated in 14 cases	
Amitriptyline	6 (43)
Tramadol	5 (36)
Valproate	5 (36)
Paroxetine	2 (14)
Sertraline	2 (14)
Citalopram	1 (7)
Fluoxetine	1 (7)

F: Female; M: Male; SD: Standard deviation; SS: Serotonin syndrome.

Case 1

A 21-year-old male was diagnosed with a primary generalized epilepsy disorder and started taking sodium valproate (1000 mg daily) about 2 years prior. Six months ago, he developed progressively increasing tremor, irritability, bradykinesia, rigidity, and gait disturbance. When asked, the patient admitted to having irritability, disturbed sleep, and intermittent diaphoresis. Physical examinations revealed tachycardia (112 beats/min), postural tremor of both hands, rigidity in the limbs, generalized hyperreflexia, and inducible ankle clonus. Haematological and biochemical investigations (including valproate level, ceruloplasmin level, urinary copper, and

thyroid function profiles) were normal. Magnetic resonance imaging brain, electroencephalography, and cerebrospinal fluid examination revealed no abnormalities. The patient fulfilled the Hunter criteria for SS. Initially, the patient refused to discontinue valproate as he was afraid of a recurrence of seizure. Cyproheptadine was started (4 mg daily) and titrated up to 4 mg three times daily. The symptoms gradually improved, and abnormal physical examinations (tachycardia, tremor, rigidity, hyperreflexia, and clonus) returned to normal in 10-12 d. Cyproheptadine was discontinued after 3 wk. However, the symptoms gradually reappeared, which again disappeared on readministration of cyproheptadine. Later, valproate was changed to levetiracetam. There was no recurrence of the similar symptoms at 9 mo follow-up.

Case 2

A 47-year-old man had been receiving amitriptyline (25 mg daily) and tramadol (50 mg twice daily) for diabetic neuropathy for about 9 mo. About 5-6 mo ago, he developed an insidiously progressive tremor of both hands, generalized body pain associated with stiffness, and sleep disturbances. The patient also reported irritability, disturbed bowel functions, dizziness, and intermittent diaphoresis. Physical examination revealed tachycardia (104 beats/min), hand tremors, rigidity in all four limbs, hyperreflexia, and ankle clonus. Haematological and biochemical investigations were normal. Magnetic resonance imaging brain and electroencephalography revealed no abnormalities. The patient fulfilled the Hunter criteria of SS. Amitriptyline and tramadol were discontinued, and cyproheptadine was administered (4 mg thrice daily). The clinical features improved significantly over 5-6 d and disappeared in 2 wk. The symptoms did not recur in the 6-mo follow-up.

Case 3

A 36-year-old man, on paroxetine (40 mg daily) and amitriptyline (25 mg daily) for obsessive-compulsive disorder for 18 mo, developed insidiously progressive upper limbs tremor and rigidity of the lower limbs associated with gait difficulty. In parallel, he had sleep disturbances, irritability, and generalized body pain. The symptoms gradually increased in the last 4-5 mo. Physical examinations revealed tachycardia (102 beats/min), coarse postural tremor of both upper limbs, rigidity in the lower limbs, generalized hyperreflexia, and ankle and knee clonus. Biochemical parameters and neuroradiological investigations were unremarkable. The patient feared a recurrence of obsessive-compulsive disorder, so we did not attempt to discontinue paroxetine and amitriptyline. He was started on cyproheptadine (4 mg thrice daily). The patient noted an almost complete improvement in 7-8 d. Cyproheptadine was discontinued after 3 wk, but symptoms reappeared in 3-4 wk. Reintroduction of cyproheptadine provided complete cessation of the symptoms. The patient preferred to continue cyproheptadine, and paroxetine and amitriptyline as well. There was no recurrence of similar symptoms in 12 mo follow-up.

DISCUSSION

All patients met the Hunter clinical criteria of SS, and at the same time, each patient showed a positive response to cyproheptadine. Therefore, we believe that these patients had SS. There was no better alternative diagnosis for any of these 14 cases, as no biochemical or other abnormalities were found in any of the patients indicating any other pathology. The disappearance of generalized body pain, insomnia, gait problems, bowel problems, dizziness, sexual dysfunctions, incoordination, and fatigue after receiving cyproheptadine suggests that this symptom complex was the part of SS spectrum. Fever and agitation are important clinical features in both criteria of SS[7,8]; however, none of our patients had any of these two symptoms. Patients with fever and agitation often seek immediate care in the hospital. As we included only chronic cases, fever and agitation were not the part of the symptom complex in our patients.

SS typically presents within 24 h of initiation or change in the dose of serotonergic agents, and it may evolve very rapidly, leading to death within a few hours[1,6]. However, mild cases of SS (tremor with hyperreflexia and hypertonia) may be ignored by patients and doctors, and patients can continue to take serotonergic drugs for a longer period. Such patients may represent the chronic variant of SS. We reviewed the literature to find cases of SS having an indolent course or chronic SS. Alnwick[3] reported a 42-year-old female patient who had been on antidepressants for a long period. She developed generalized body pain, including headaches, and received a

diagnosis of fibromyalgia. Unfortunately, she received several additional serotonergic agents over the years. A careful observation raised the possibility of SS, and the discontinuation of the offending drugs led to complete improvement. Lamberg *et al*[4] reported a 41-year-old woman who received various serotonergic agents over the years for generalized body pain. She developed various other symptoms over the years, including aggravation of pain, hand tremors, dyskinesia, and insomnia. A detailed examination revealed the presence of clonus, hyperreflexia, and tremor, fulfilling the Hunter criteria of SS[4]. Chechani[9] reported a patient who had four episodes of SS over 3-4 years. In one episode, tremors persisted for 6 wk before the development of full-blown SS. Moreover, tremors and muscle pain persisted for about 2 mo, even after the withdrawal of the serotonergic agent (fluoxetine). This case highlights that tremors and myalgia may persist for a long period. Prakash *et al*[5] reported a patient who had been on various serotonergic agents for more than 2 years after a road traffic accident. He developed various new symptoms, which were considered to be sequelae of the road traffic accident. A detailed examination suggested a possibility of SS, and discontinuation of serotonergic agents and administration of cyproheptadine led to complete resolution of the symptoms.

In the present case series, we included those patients in whom the disease started insidiously, and the duration of illness was longer (mean duration of illness-13.5 wk, range: 6-24 wk), indicating a chronic pattern. Generalized body pain, stiffness of the limbs, insomnia, dizziness, and irritability were the common presenting features. Such nonspecific symptoms are often ignored by patients, and even physicians do not take these symptoms seriously and attribute such symptoms to underlying primary disorders or associated somatic complaints or nonspecific drug-induced side effects. Several studies have reported tremors and other nonspecific symptoms as common side-effects of serotonergic agents. However, these studies are silent regarding the presence or absence of hyperreflexia and clonus. Such side effects are frequently misdiagnosed as drug-induced tremors, drug-induced parkinsonism, or extrapyramidal syndrome. Five patients in our series received sodium valproate. Sodium valproate is known to cause SS, parkinsonism, and isolated tremor. In Armon *et al*[10] case series on valproate-induced parkinsonism, approximately 44% of patients had upper motor neuron (UMN) signs. Cognitive disturbances are also very common in valproate-induced parkinsonism. Autonomic features have also been noted in some cases of valproate-induced parkinsonism[11]. Therefore, a subset of valproate-induced parkinsonism patients may also satisfy the Hunter criteria. In addition, most of the cases of valproate-induced parkinsonism have insidious onset and chronic course. Therefore, the possibility of chronic SS exists in a subset of patients with valproate-induced parkinsonism. Various selective serotonin reuptake inhibitors and other serotonergic agents are known to cause tremors and parkinsonism-like symptoms[12,13]. Most of these observations did not mention anything about UMN signs. Since examination for clonus is not a regular phenomenon in clinical practice, it is possible that a subset of such patients may have hyperreflexia or inducible clonus, fulfilling the criteria of SS. So, the number of actual cases of chronic cases of SS may be much higher than the actual reported cases in the literature.

The clinical manifestations of SS depend on the degree of elevation of the intrasynaptic concentration of serotonin. The mild elevation of serotonin in the central nervous system leads to hyperreflexia, inducible clonus, tremors, anxiety, and restlessness[2]. The most important feature in the Hunter criteria is the presence of upper motor signs (spontaneous clonus, inducible clonus, hyperreflexia, and hypertonia). Unfortunately, the Hunter criteria are silent about the UMN related symptoms or complaints. Hypertonia and other UMN signs typically induce musculoskeletal complaints, such as pain, stiffness, slowness in the movement, tiredness, and fatigue[14]. We hypothesize that mildly elevated serotonin for a long period in the central nervous system will induce sustained UMN symptoms and signs. Persistent hypertonia or spasticity usually manifests as stiffness/rigidity, muscle pain, and functional disability. This may be a possible explanation for the presence of generalized body pain, stiffness of the limbs, gait problems, and fatigue noted in our observations and other case series. Irritability, dizziness, and insomnia may be related to mild cognitive abnormalities due to raised intrasynaptic serotonin concentration[2].

Although SS typically develops rapidly after ingestion of serotonergic drugs, our observations suggest that a subset of patients may have mild and chronic forms. A diagnosis of SS is important even in mild and indolent form, as it is not supposed to resolve spontaneously as long as serotonergic drugs are administered. Furthermore, it may progress rapidly to death by an inadvertent increase of the dose or addition of another serotonergic agent.

Limitations

This report is a retrospective study and a possibility of unrecognized selection bias exists. We reviewed the clinical features in patients with insidious onset SS. So, these are not truly representative of typical cases of SS. Although all patients fulfilled the Hunter criteria, we cannot rule out a possibility of other causes as the full evaluation was not done on each patient.

CONCLUSION

SS is not rare in clinical practice. However, various aspects of this syndrome need to be explored. Herein, we suggest that chronic SS is not rare in clinical practice, and patients may present with non-specific clinical symptoms. We suggest that patients who are on serotonergic drugs should be physically examined for the presence of clonus and other related signs upon the development of any new symptom to rule out SS.

ARTICLE HIGHLIGHTS

Research background

Serotonin syndrome (SS) is a life-threatening condition, and the clinical features largely depend on the degree of elevation of the intrasynaptic concentration of 5-hydroxytryptamine or serotonin. Mild elevation of serotonin levels causes mild serotonin toxicity and manifest as hyperreflexia, inducible clonus, tremors, anxiety, and restlessness. We hypothesize that mild SS may remain unnoticed for a longer duration and will manifest as insidious onset nonspecific symptoms.

Research motivation

Only very limited data are available about chronic SS. We believe that the diagnosis of chronic SS is important. Increasing the dose of a serotonergic agent or adding another serotonergic agent to a patient with chronic SS can be serious and fatal.

Research objectives

To describe the epidemiological, clinical, and other aspects of chronic SS.

Research methods

We retrospectively evaluated 14 consecutive adult patients (> 18 years) who had presenting complaints for more than 6 wk at the time of the first consultation and fulfilled the Hunter criteria of SS.

Research results

We identified 19 patients who met the inclusion criteria. Five patients were excluded for various reasons, and finally, the records of 14 cases were analysed. The mean age was 41.1 years (range: 21-61 years), with a male preponderance (64%). Generalized body pain, insomnia, and restlessness were common presenting features. The mean duration of symptoms before getting the diagnosis of SS was 13.5 ± 5.8 wk. Amitriptyline was the most common drug, followed by tramadol and sodium valproate. The response to cyproheptadine was satisfactory in all patients.

Research conclusions

Patients with chronic SS may have nonspecific symptoms. A detailed drug history and thorough physical examinations are essential to clinch the cases of chronic SS.

Research perspectives

The incidence of SS is increasing because of the widespread use of serotonergic drugs. There is a need to improve the awareness about SS among the physicians for early recognition and effective management.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 April 19; 11(4): 133-152

DOI: 10.5498/wjp.v11.i4.133

ISSN 2220-3206 (online)

META-ANALYSIS

Effectiveness of digital psychotherapeutic intervention among perinatal women: A systematic review and meta-analysis of randomized controlled trials

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Author contributions: Lau Y conceived and guided the study; Cheng JY, Wong SH and Yen KY carried out the literature searches; Cheng JY and Yen KY extracted the data; Cheng JY and Yen KY assessed the study quality; Lau Y, Wong SH, and Cheng LJ performed the statistical analysis; Lau Y wrote the manuscript; Lau Y, Cheng JY, Wong SH, Yen KY and Cheng LJ revised the manuscript.

Supported by Ministry of Education Academic Research Fund (AcRF) Tier 1, No. NUHSRO/2017/054/T1.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an

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Abstract

BACKGROUND

The perinatal period is a challenging time of substantial emotional, physiological, social, and relational changes. Depression, anxiety, and stress symptoms are common, and co-exist in the perinatal period. Digital technology continues to grow at an unprecedented pace with wide application, including psychotherapeutic intervention. A growing number of meta-analyses supported the application of digital psychotherapeutic intervention across different populations, but relatively few meta- and meta-regression analyses have concentrated on perinatal women.

AIM

To evaluate the effectiveness of digital psychotherapeutic intervention on improving psychological outcomes among perinatal women and identify its essential features.

METHODS

Randomized controlled trials (RCTs) were obtained from eight databases, including Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Embase, Scopus, PsycINFO, PubMed, Web of Science, and ProQuest Dissertation and Theses from inception up until November 24, 2020. Comprehensive Meta-analysis 3.0 software was used to conduct meta- and meta-regression analyses. The Cochrane risk-of-bias tool and the Grading of the Recommendation, Assessment, Development, and Evaluation system were adopted to assess the individual and overall qualities of the evidence, respectively.

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Manuscript source: Invited manuscript

Specialty type: Obstetrics and gynecology

Country/Territory of origin: Singapore

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 30, 2020
Peer-review started: December 30, 2020
First decision: January 11, 2021
Revised: January 11, 2021
Accepted: March 10, 2021
Article in press: March 10, 2021
Published online: April 19, 2021

P-Reviewer: Feng QS, Lee PN
S-Editor: Zhang L
L-Editor: A
P-Editor: Li JH

RESULTS

A total of 25 RCTs that included 3239 women were identified. Meta-analyses revealed that intervention significantly improved depression (Hedges's g = 0.49), anxiety (g = 0.25), and stress (g = 0.47) symptoms compared to the control. Subgroup analyses demonstrated that a website platform with ≥ eight therapist-guided sessions using the theoretical principle of cognitive behavioral therapy was more effective than other treatments in improving depression symptoms in postnatal women. Meta-regression analyses observed that the age of perinatal women and the type of psychotherapy also had statistically significant effects on depression symptoms. Egger's regression asymmetry tests suggested that no publication biases occurred, but the overall quality of the evidence was very low.

CONCLUSION

This review suggests that digital psychotherapeutic intervention may be a potential solution to reduce psychological problems in perinatal women. Further high-quality RCTs with large sample sizes are needed.

Key Words: Digital psychotherapeutic intervention; Perinatal women; Meta-analysis; Meta-regression

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Core Tip: This systematic review identified and analyzed the findings of 25 randomized controlled trials, and the results indicated that digital psychotherapeutic intervention could significantly reduce depression, anxiety, and stress symptoms among perinatal women. The essential features of this intervention were a website platform with ≥ eight therapist-guided sessions using the cognitive behavioral therapy theoretical principle. This intervention was also effective in reducing depression symptoms when treating young postnatal women. The overall evidence grade of outcomes was very low according to the Grading of Recommendations, Assessment, Development, and Evaluation criteria. Thus, future trials need to include a high-quality design and a large sample size.

Citation: Lau Y, Cheng JY, Wong SH, Yen KY, Cheng LJ. Effectiveness of digital psychotherapeutic intervention among perinatal women: A systematic review and meta-analysis of randomized controlled trials. *World J Psychiatr* 2021; 11(4): 133-152
URL: https://www.wjgnet.com/2220-3206/full/v11/i4/133.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i4.133

INTRODUCTION

Perinatal period is a challenging time of substantial emotional, physiological, social, familial, and role changes[1,2]. These changes may affect psychological and physical resources, resulting in increased susceptibility of psychological problems, including depression, anxiety, and stress[3]. A systematic review observed that depression, anxiety, and stress symptoms co-existed in the perinatal period[4]. The prevalence in the perinatal period was estimated to be 7.4%-12.8% for depressive disorders[5], 3%-6% for anxiety disorders[6], and 3.3%-4.0% for posttraumatic stress disorders[7]. Perinatal mental disorders during pregnancy and postpartum period are associated with considerable maternal, infant, and child morbidity and mortality[8-10]. In addition, they lead to huge economic burden on health and social care[3]. Therefore, effective intervention is imperative. Psychotherapeutic intervention is considered a highly effective intervention for depression, anxiety, and stress[11].

Psychotherapeutic interventions are based on several principles, including cognitive behavioral therapy (CBT)[12], mindfulness therapy[13], problem-solving therapy[14], stress-reduction therapy[15], psychoeducation intervention[16], or their combination. The assumption of CBT is that dysfunctional cognitive patterns result in emotional distress and subsequent maladaptive behavior[12]. CBT aims to improve psychological outcomes by helping women learn how to recognize and modify destructive thought

patterns[12]. Mindfulness therapy suggests that negative psychological outcomes are due to automatic reaction[13]. It works by training women to react to things differently, and it involves the awareness of existing thoughts, emotions, and sensations to cultivate acceptance of every moment[13].

The core assumption of problem-solving therapy is that psychological symptoms are generated when women become overwhelmed by practical problems they face in their daily lives[14]. This type of therapy aims to help perinatal women by teaching structured means to solve their problems, which in turn alleviate their psychological outcomes[14]. Stress-reduction therapy focuses on stress management that helps women develop skills to manage, cope with, and reduce stress to promote well-being[15]. Psychoeducation intervention integrates and synergizes psychotherapeutic and educational components to help women deal with problems[16]. Psychoeducational techniques are used to improve awareness of cognitive distortions, communication, and problem-solving skills by providing information in a proactive fashion[16].

Empirical evidence suggests that CBT[17], mindfulness therapy[18], problem-solving therapy[19], stress-reduction therapy[20], and psychoeducation intervention[21] using face-to-face approach is effective in improving psychological outcomes among perinatal women. However, traditional face-to-face psychotherapeutic interventions may reduce effectiveness due to structural and psychological barriers[22-24]. Structural barriers include insufficient mental health professionals, difficulties booking appointments, and transportation problems[24,25]. Psychological barriers could arise due to the lack of motivation and self-stigmatization to seek treatment or overestimated barriers to seek treatment[26,27].

Digital technology continues to grow at an unprecedented pace with wide application, including psychotherapeutic intervention[28,29]. Psychotherapeutic intervention is considered as digital when technology, such as website, mobile application, email, or text messaging services, is used in its delivery[28]. Given that 80% of the population own mobile phones and 50% have access to the Internet[30], the use of digital technology in psychotherapeutic interventions has increased rapidly over the past several years[28]. Digital psychotherapeutic interventions essentially allow for improved connectivity, accessibility, and availability of support[31]. With the interventions being delivered online, a potential exists for a larger audience to receive these interventions because they could likely be accessed regardless of geographical location[31]. The option of implementing online programs helps mitigate the problem of insufficient healthcare professionals and reduce waiting times[22]. Thus, digital psychotherapeutic interventions could be comparatively more cost effective than other interventions[32]. Another important benefit is that digital psychotherapeutic interventions may be more attractive to individuals who may not feel comfortable with being out in public places or are reluctant to seek treatment due to social stigma[33].

Digital psychotherapeutic intervention aims at alleviating psychological symptoms with different assumptions and mechanisms in accordance with the different principles of psychotherapy. Figure 1 illustrates the possible mechanisms by which digital psychotherapeutic intervention could improve depression, anxiety, and stress symptoms in perinatal women. These mechanisms were proposed by extracting the frameworks of CBT[12], mindfulness therapy[13], problem-solving therapy[14], stress-reduction therapy[15], and psychoeducation intervention[16]. Perinatal women experienced psychological problems due to dysfunctional thoughts[12], automatic reaction[13], being overwhelmed by problems[14], perceived stress[15], and knowledge deficit[16]. They may learn how to modify destructive thought patterns[12], improve awareness[13], solve problems[14], reduce stress[15], and enhance their knowledge[16]. The use of digital technology could improve the connectivity, accessibility, and flexibility of psychotherapeutic intervention in accordance with a wide array of functions of digital platform[28,29,31]. Besides, the digitalization of psychotherapy could reduce time strain, stigma, and personnel costs[22,32,33]. Consequently, perinatal women may alleviate their depression, anxiety, and stress symptoms.

A growing number of systematic reviews[28,34,35] have supported the effectiveness of digital psychotherapeutic intervention among college students[35], patients with serious mental illness[34], and young adults[28]. However, relatively little is known about its effectiveness in the perinatal population. Previous reviews[36-38] have investigated the potential effect of digital psychotherapeutic intervention among perinatal women. However, these reviews were limited to few selected trials[37,38], a mixture of different research designs[36-38], few databases[37], and only narrative synthesis[37]. None of these reviews investigated the preferred features and the overall evidence. In addition, none of them used meta-regression analysis to assess the influence of covariates on their effect size. Thus, the effectiveness and essential features of digital psychotherapeutic

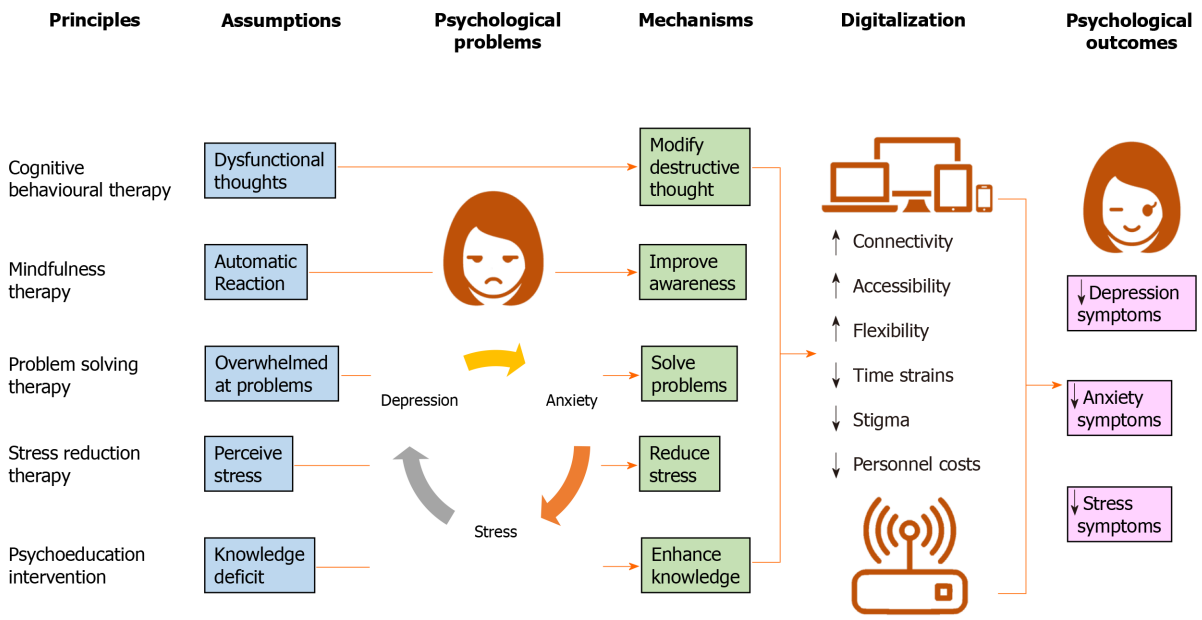


Figure 1 Potential mechanisms of digital psychotherapeutic intervention in improving psychological outcomes.

intervention among perinatal women remain unclear.

In light of the abovementioned limitations of the existing systematic reviews[36-38], the present review aims to synthesize the best evidence to (1) assess the effectiveness of digital psychotherapeutic intervention in reducing depression, anxiety, and stress symptoms; (2) evaluate the preferred design features of the intervention.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was followed[39]. This review was registered in the PROSPERO database at the Centre of Reviews and Dissemination in the United Kingdom (CRD42021226534).

Eligibility criteria

All types of randomized controlled trials (RCTs) were included because of the strongest empirical evidence of the intervention's effectiveness[40]. Published and unpublished trials in the English language without restriction to publication year were included to maximize the search scope. A description of the eligibility criteria is summarized in Supplementary Table 1. The RCTs were selected on the basis of their fulfilment of the Participants, Interventions, Comparisons, Outcomes, and Study design framework[39]. The population involved perinatal women aged 18 years and older from the start of pregnancy to first-year postpartum. The psychotherapeutic interventions were included if the content design was based on the CBT theoretical principle[12], mindfulness therapy[13], problem-solving therapy[14], stress-reduction therapy[15], psychoeducation intervention, or their combination and if they were delivered *via* website or/and mobile application[28]. The comparators or counterparts consisted of treatment as usual, waitlist control, or placebo control. Outcomes were depression, anxiety, and stress symptoms.

Searching strategies

A scoping search was conducted in the Cochrane Central Register of Controlled Trials, Joanne Briggs Institute Evidence Synthesis, and PROSPERO databases to prevent duplication of similar systematic reviews. A senior librarian was consulted regarding the search strategy. A comprehensive three-step search strategy was conducted in congruence with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[41]. First, a search of published literature up until November 24, 2020 was conducted using keyword and index terms in eight electronic databases as follows: Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Embase, Scopus, PsycINFO, PubMed, Web of Science, and ProQuest

Dissertation and Theses, as shown in Supplementary Table 2. Next, ongoing trials from various clinical trial registries (ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and ISRCTN Registry) were explored. Lastly, the bibliographies of RCTs and systematic reviews were hand-searched using snowballing. In addition, specific journals and different grey literature resources (Google Scholar and GreySource) were checked to ensure the comprehensiveness of the search[42].

Study selection

Study selection was conducted in accordance with the PRISMA flow diagram[39]. EndNote X9 (version 9.3.3) software[43] was used to import all identified citations and remove duplicates. After records from the databases were identified, two independent reviewers (JYC and KYY) screened the titles and abstracts for relevance. Full-text articles of eligible studies were retrieved and examined by the two reviewers independently on the basis of eligibility criteria. Differing responses were discussed and referred to a third reviewer (YL). Reasons for excluding trials in the full-text screening stage were recorded. A Kappa statistic (κ) larger than 0.6 was computed to determine an acceptable inter-rater agreement[44].

Data extraction

A standardized data extraction form was developed and piloted in accordance with the Cochrane Handbook for Systematic Reviews of Intervention[41]. The items extracted in relation to the characteristics of the trials included study setting, city/country, study design, sample size, participants' age (mean and standard deviation), sample size, intervention (name), comparator, outcome (measure), attrition rate, grant support, intention to treat (ITT), missing data management, published protocol, and registration. The items involving digital psychotherapeutic intervention included aim, types, component, platform, regime (length, number of sessions, frequency, duration, and follow-up), guidance (from therapist/self), and theoretical basis. Dichotomous or continuous psychological outcomes, such as depression, anxiety, and stress symptoms at post-intervention, were extracted. The authors of the selected trials were contacted to obtain unpublished data or clarify questionable information.

Quality assessment

The Cochrane Collaboration risk-of-bias tool[45] was adopted to individually evaluate the quality of the trials. Two reviewers (JYC and KYY) conducted the assessments independently to minimize errors[41]. Selection, performance, detection, attrition, and reporting biases were assessed using the following six domains: (1) Random sequence generation; (2) Allocation concealment; (3) Participant and personnel blinding; (4) Outcome assessment blinding; (5) Incomplete outcome data; and (6) Selective reporting. The risk for each author was graded as low, high, or unclear. The attrition rate, ITT, missing data management, published protocol, and registration of selected trials were investigated to further assess the quality of evidence.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) checklist[46] was adopted to judge the overall quality and strength of the recommendations by using GRADEpro 3.6 software[47]. The overall evidence was graded as high, moderate, low, or very low in accordance with five aspects: Methodological limitations, inconsistency, indirectness, imprecision, and publication bias[48]. Publication bias was evaluated through visual inspection of the funnel plot asymmetry[49] and Egger's test[50] when each outcome included 10 or more trials.

Statistical analysis

Comprehensive Meta-Analysis software (version 3)[51] was used for meta-analyses. The random-effect model was also used because it accounts for the statistical assumption of variation in the estimation of mean across all trials[52]. The overall effect was computed using Z-statistics at a significance level of $P < 0.05$. The pooled mean effect sizes of psychological outcomes were estimated using Hedges' g, which provides an accurate estimation of the overall effect size when the included trials have small sample sizes[53]. The effect size was interpreted as small (0.2), medium (0.5), large (0.8), and very large (1.2)[54].

The inverse-variance statistical method was utilized to compute continuous outcomes[41]. Heterogeneity was evaluated on the basis of the Cochran Q test, in which $P < 0.10$ indicates the presence of significant statistical heterogeneity[41]. The I^2 statistic was used to quantify the degree of heterogeneity, in which I^2 indicates the variation percentage[55], such as 0%-40% (may not be important), 30%-60% (moderately

important), 50%-90% (substantially important), and 75%-100% (considerably important)[56].

Additional analysis

Sensitivity analyses were conducted to identify heterogeneous trials that were removed to maintain overall homogeneity[57]. Subgroup analyses were also performed to reduce the overall heterogeneity across studies (I^2 > 40%)[58] and compare the effects among various populations, settings, and features of intervention[59]. The predefined subgroups included population nature, theoretical principle, digital platform, aim of intervention, guidance, and number of sessions.

Meta-regression analysis was conducted to explain whether the heterogeneity between trials could be attributed to covariates[60]. A random-effect meta-regression model was used to assess if the year of publication, mean age, sample size, type of psychotherapy, number of sessions, and duration influenced the effect size of digital psychotherapeutic intervention. A significance level of P < 0.05 was used for the random-effect meta-regression analysis. Narrative synthesis of outcomes was performed when meta-analysis could not be conducted on the data.

RESULTS

Study selection

Figure 2 illustrates a PRIMSA flowchart of the selection of trials. A total of 34249 articles were identified from eight databases, and 8046 duplicates were removed using Endnote. Six additional records obtained from snowballing were included. After screening was conducted by two independent reviewers (JYC and KYY), 26167 articles were excluded in accordance with their titles and abstracts, and 42 full-test articles were selected for eligibility. Twenty-five RCTs were eventually selected. Among them, 24 were international peer-reviewed articles[61-84] and one was an unpublished doctoral dissertation[85]. Moderate agreement was reached between the dyad raters (κ = 0.78).

Characteristics of included randomized controlled trials

Table 1 summarizes the characteristics of 3239 perinatal women in the 25 included RCTs from 2009[85] to 2020[77] in Australia[73,75], Canada[81], China[84], Germany[70,71], Iran[67], Netherlands[66,76,76], Portugal[64], Scotland[72], Singapore[68], Sweden[65,74,78], Switzerland[82,83], the United States of America[62,63,69,85], the United Kingdom[79,80], and 23 countries[61]. The RCTs were two armed (k = 22) or three armed (k = 3)[67,68,74]. They were conducted in hospital (k = 2)[68,84] or in the community (k = 23). The populations studied included healthy antenatal[61,62,74,76,77] and postnatal[68,85] women and women who experienced psychological problems[64-67,73,75,77-81,84], insomnia[63,69], preterm labor[82,83], miscarriage[72], or pregnancy loss[70,71]. The sample size ranged from 25[62] to 910[80]. The mean age was between 27.7[67] and 34.6[78] years.

Risk of bias

A risk-of-bias summary is shown in Supplementary Figure 1 with moderate inter-rater agreement (κ = 0.72). Among the 25 included RCTs, 53.33% had low risk of bias across six domains. More than half (56%) had unclear allocation concealment. The participants and personnel in the majority of trials were not blinded (92%). Assessment of the outcomes was also not blinded in most trials (72%). Eleven RCTs[61,70-72,74,78-80,84,85] did not have published protocols nor were registered in any clinical trial registry. Therefore, 44% of the reported bias was unclear. The attrition rates ranged from 1.1%[69] to 66.1%[61]. The majority of trials used ITT analysis (68%) and mentioned missing data management (60%).

Digital psychotherapeutic intervention

A detailed description of digital psychotherapeutic intervention for the 25 trials is presented in Supplementary Table 3. The aims of intervention were divided into prevention and treatment using CBT principles, mindfulness therapy, problem-solving therapy, stress-reduction therapy, psychoeducation intervention, or the combined version. The interventions were mainly delivered *via* website (k = 22) or mobile application (k = 4)[63,67,77,84], and some of them were supplemented with email, phone call, short messaging service, or home visit. The elements consisted of counselling, education, advice, assignment, feedback, reminder, forum, support, self-monitoring, questions, and answers. The interventions lasted between 10[62] and 90[61] min and

Table 1 Characteristics of selected 25 randomised controlled trials

Ref.	Country/setting	Design	Population (nature)	Age (mean ± SD)	Intervention (name)	Comparator	Sample size	Outcome (Measures)	Attrition rate (%)	ITT/MDM	Protocol/registry	Grant
Barrera *et al*[61], 2015	23 countries/Community	2-arm RCT	Antenatal (mixed trimesters)	30.2 ± 5.6	Mood management internet intervention (Curso Internet de Mamás y Bebés)	Placebo (Information only)	I: 57; C: 54	Depression symptoms (CES-D)	66.1%	No/No	No/No	Yes
Duffecy *et al*[62], 2019	United States/Community	2-arm RCT	Antenatal (20–28 wk)	30.5 ± 4.1	Share (group) condition (Sunnyside)	Placebo (individual) condition	I: 18; C: 7	Depression symptoms (PHQ-8 and HDRS)	28%	No/No	No/Yes	Yes
Felder *et al*[63], 2020	United States/Community	2-arm RCT	Antenatal (≤ 28 wk, insomnia by SCI, EPDS ≥ 15)	33.6 ± 3.7	Digital cognitive behavioural therapy for insomnia (Sleepio)	Treatment as usual	I: 105; C: 103	Depression symptoms (EPDS), Anxiety symptoms (GAD-7)	11.1 %	Yes/No	No/Yes	Yes
Fonseca *et al*[64], 2019	Portugal /Community	2-arm RCT	Postnatal women (PDPI-R ≥ 5.5 or EPDS > 9	32.6 ± NR	Web-based intervention (Be a Mom)	Waitlist	I: 98; C: 96	Depression symptoms (EPDS)	24.2 %	Yes/Yes	No/Yes	Yes
Forsell *et al*[65], 2017	Sweden/Community	2-arm RCT	Antenatal (10-28 wk, major depression by SCID; MADRS-S: 15-35)	31.0 ± NR	Internet-delivered cognitive behaviour therapy (ICBT)	Treatment as usual	I: 22; C: 20	Depression symptoms (EPDS and MADRS-S), Anxiety symptoms (GAD-7)	7.1 %	Yes/Yes	No/Yes	Yes
Heller *et al*[66], 2020	Netherlands /Community	2-arm RCT	Antenatal (< 30 wk with CES-D ≥ 16, HADS-A ≥ 8)	32.0 ± NR	Internet- based problem-solving treatment (MamaKits Online)	Treatment as usual	I: 79; C: 80	Depression symptoms (EPDS and CES-D), Anxiety symptoms (HADS-A)	17.6%	Yes/Yes	Yes/Yes	Yes
Jannati *et al*[67], 2020	Iran/Community	3-arm RCT	Postnatal (≤ 6 mo, EPDS ≥ 13 and MINI)	27.7 ± 4.2	App-based cognitive behavioural therapy (Happy Mom)	Treatment as usual	I: 39; C: 39	Depression symptoms (EPDS)	3.9%	No/No	No/Yes	Yes
Jiao *et al*[68], 2019	Singapore/Hospital	3-arm RCT	Postnatal (first time mother < 6 wk)	30.7 ± NR	Web-based psychoeducational intervention (NR)	Treatment as usual	I: 68; C: 68	Depression symptoms (EPDS)	6.9%	Yes/Yes	Yes/Yes	Yes
Kalmbach *et al*[69], 2020	United States/Community	2-arm RCT	Antenatal (27.76 ± 0.87 wk with insomnia using ISI ≥ 10 and EPDS ≥ 19)	29.0 ± 4.2	Digital cognitive behavioural therapy for insomnia (Sleepio)	Placebo (Digital sleep education)	I: 46; C: 45	Depression symptoms (EPDS)	1.1%	Yes/Yes	No/Yes	Yes
Kersting *et al*[71], 2011	Germany/Community	2-arm RCT	Postnatal (loss of child with 5-43 wk)	34.3 ± 5.3	Internet-based cognitive behavioural treatment programme (NR)	Waitlist	I: 45; C: 33	Depression symptoms (GSI-D), Anxiety symptoms (GSI-A) Stress symptoms (IES)	22.9%	Yes/Yes	No/No	Yes

Kersting *et al*[70], 2013	Germany/Community	2-arm RCT	Postnatal (loss of child with 2-40 wk)	34.2 ± 5.2	Internet-based cognitive behavioural treatment programme (NR)	Waitlist	I: 115; C: 113	Depression symptoms (GSI-D) Anxiety symptoms (GSI-A) Stress symptoms (IES-R)	12.7%	Yes/No	No/No	Yes
King *et al*[85], 2009	United States/Community	2-arm RCT	Postnatal (≤ 12 mo)	32.5 ± NR	Internet-based stress management program (LivingSmart)	Face- to-Face control group	I: 28; C: 29	Depression symptoms (BDI-II), Anxiety symptoms (STAI) Stress symptoms (PSS)	33.1%	No/No	No/No	Yes
Klein *et al*[72], 2012	Scotland/Community	2-arm RCT	Postnatal (Miscarriage with < 24 wk)	33.0 ± 6.3	Web-based intervention (Miscarriage matters)	Treatment as usual	I: 33; C: 34	Depression symptoms (HADS-D), Anxiety symptoms (HADS-A)	35.8%	Yes/Yes	No/No	Yes
Loughnan *et al*[73], 2019	Australia/Community	2-arm RCT	Antenatal (13-30 wk, GAD-7 > 9 and/or PHQ-9 > 9)	31.6 ± 4.0	Internet-delivered cognitive behavioural therapy program (MUMentum Pregnancy)	Treatment as usual	I: 43; C: 44	Depression symptoms (EPDS), Anxiety symptoms (GAD-7) Stress symptoms (K-10)	11.5%	Yes/Yes	Yes/Yes	Yes
Matvienko-Sikar *et al*[74], 2017	Sweden/Community	3-arm RCTs	Antenatal (10-22) wk	33.8 ± 3.0	Novel positive psychological intervention (BodyScan and Reflection)	Treatment as usual	I: 32; C: 14	Depression symptoms (EPDS) Stress symptoms (PDQ)	6.5%	No/No	No/No	No
Milgrom *et al*[75], 2016	Australia/Community	2-arm RCT	Postnatal (< 12 mo, EPDS 11-23)	31.6 ± NR	Internet cognitive behavioural therapy (MumMoodBooster)	Treatment as usual	I: 21; C: 22	Depression symptoms (BDI-II), Anxiety symptoms (DASS-21-A), Stress symptoms (DASS-21-S)	6.9%	Yes/Yes	No/Yes	Yes
Missler *et al*[76], 2020	Netherlands/Community	2-arm RCT	Antenatal (26-34 wk)	32.5 ± NR	Psycho-educational Intervention (NR)	Waitlist	I: 68; C: 69	Depression symptoms (EPDS), Anxiety symptoms (HADS-A), Stress symptoms (PSI)	11.7%	Yes/Yes	Yes/Yes	Yes
Molenaar *et al*[77], 2020	Netherlands/Community	2-arm RCT	Antenatal (12-16 wk, depression history)	32.2 ± 4.9	Discontinuation of anti-depressants with Preventive Cognitive Therapy (STOP)	Treatment as usual	I: 24; C: 20	Depression symptoms (EPDS and HDRS), Anxiety symptoms(STAI)	13.6%	No/No	Yes/Yes	Yes
Nieminen *et al*[78], 2016	Sweden/Community	2-arm RCT	Postnatal (≥ 3 mo, TES ≥ 30)	34.6 ± 4.8	Internet-based trauma-focused cognitive behaviour therapy (TF-ICBT)	Waitlist	I: 28; C: 28	Depression symptoms (BDI-II and PHQ-9), Anxiety symptoms (BAI), Stress symptoms (IER-R)	9.8%	Yes/Yes	No/No	Yes
O'Mahen *et al*[80], 2013	United Kingdom/Community	2-arm RCT	Postnatal (< 12 mo, EPDS > 12)	32.3 ± NR	Internet-based behavioral activation (Netmums)	Treatment as usual	I: 462;C: 448	Depression symptoms (EPDS)	61%	Yes/No	No/No	Yes
O'Mahen	United	2-arm	Postnatal (< 12	32.3 ± NR	Internet behavioral	Treatment as	I: 41; C: 42	Depression symptoms	13.2%	Yes/Yes	No/No	Yes

et al[79], 2014	Kingdom/Community	RCT	mo, EPDS > 12)		activation treatment (NetmumsHWD)	usual		(EPDS), Anxiety symptoms (GAD-7)			
Pugh *et al*[81], 2016	Canada/Community	2-arm RCT	Postnatal (< 12 mo, EPDS ≥ 10)	≥ 18 ± NR	Therapist assisted, Internet-delivered cognitive behavior therapy (TA-ICBT)	Waitlist	I: 25; C: 25	Depression symptoms (DASS-21-D), Anxiety symptoms (DASS-21-A), Stress symptoms (DASS-21-S)	18%	Yes/Yes	No/Yes	Yes
Scherer *et al*[82], 2016	Switzerland/Community	2-arm RCT	Postnatal (preterm labour with 18-32 wk)	32.7 ± 3.0	Internet-based cognitive behavioral stress management (IB-CBSM)	Placebo (Limited support)	I: 51; C: 42	Anxiety symptoms (STAI-S), Stress symptoms (PSS)	37.6%	No/No	No/Yes	Yes
Urech *et al*[83], 2018	Switzerland/Community	2-arm RCT	Postnatal (preterm labour with 18-32 wk)	32.6 ± 3.7	Internet-based cognitive behavioral stress management (IB-CBSM)	Placebo (Generic information)	I: 50; C: 43	Depression symptoms (EPDS), Anxiety symptoms(STAI-S and PRA), Stress symptoms (PSS)	44.1%	No/Yes	No/No	Yes
Yang *et al*[84], 2019	China/Hospital	2-arm RCT	Antenatal (24-30 wk, GAD-7 > 4 or PHQ-9 > 4)	30.9 ± NR	Online mindfulness intervention (NR)	Placebo (Wechat)	I: 62; C: 61	Depression symptoms (PHQ-9), Anxiety symptoms (GAD-7)	13.8%	Yes/Yes	No/No	Yes

BAI: Beck anxiety inventory; BDI-II: Beck depression inventory-II; C: Control; CES-D: Center for epidemiological studies depression; CES-D: Centre for epidemiologic studies-depression scale; DASS-21-A: Depression, anxiety and stress scales-21- anxiety subscale; DASS-21-D: Depression, anxiety and stress scales-21- depression subscale; DASS-21-S: Depression, anxiety and stress scales-21- stress subscale; EPDS: Edinburgh postnatal depression scale; GAD-7: Generalized anxiety disorder scale; GSI-A: Global severity index-anxiety subscale; GSI-D: Global severity index-depression subscale; HADS-A: Hospital anxiety and depression scale-anxiety subscale; HADS-A: Hospital anxiety and depression scale-anxiety subscale; HADS-D: Hospital anxiety and depression scale-depression subscale; HDRS: Hamilton depression rating scale; I: Intervention; IES: Impact of event scale; IES-R: Impact of event scale-revised; ISI: Insomnia severity index; ITT: Intention-to-treat analysis; K-10: Kessler psychological distress 10-item scale; MADRS-S: Montgomery-Asberg depression rating scale self-report version; MDM: Missing data management; MINI: International neuropsychiatric interview; NR: Not reported; PDPI-R: Postpartum depression predictors inventory-revised; PDQ: Prenatal distress scale; PHQ-8: Patient health questionnaire-8; PRA: The pregnancy related anxiety test; PSI: Parenting stress index; PSS: Perceived stress scale; RCT: Randomised controlled trial; SCI: Sleep condition indicator; SCI-I: Structural clinical interview for DSM Axis I disorders; STAI: State trait anxiety inventory; STAI-S: Spielberger state trait anxiety inventory; TES: Traumatic event scale.

ranged from three sessions[73] to 12 sessions[79] for 3[74]-15[80] wk. They were either self-guided (k = 7)[61,64,65,67,73,83,85] or therapist-guided (k = 18). The majority of them reported follow-up assessment (k = 19) a using theoretical basis (k = 23).

Depression symptoms

A total of 19 RCTs[62,65-76,78-81,84,85] considered depression symptoms as the outcome among 1736 perinatal women by using various measures. Meta-analysis results observed that digital psychotherapeutic intervention had a medium effect size (g = 0.49) in alleviating depression symptoms significantly (Z = -3.75, P < 0.001) compared with the control. Figure 3 illustrates the pooled results of meta-analysis using the random-effect model. Sensitivity and subgroup analyses were conducted given the considerable heterogeneity (I^2 = 84.41). However, the heterogeneity remained unexplained.

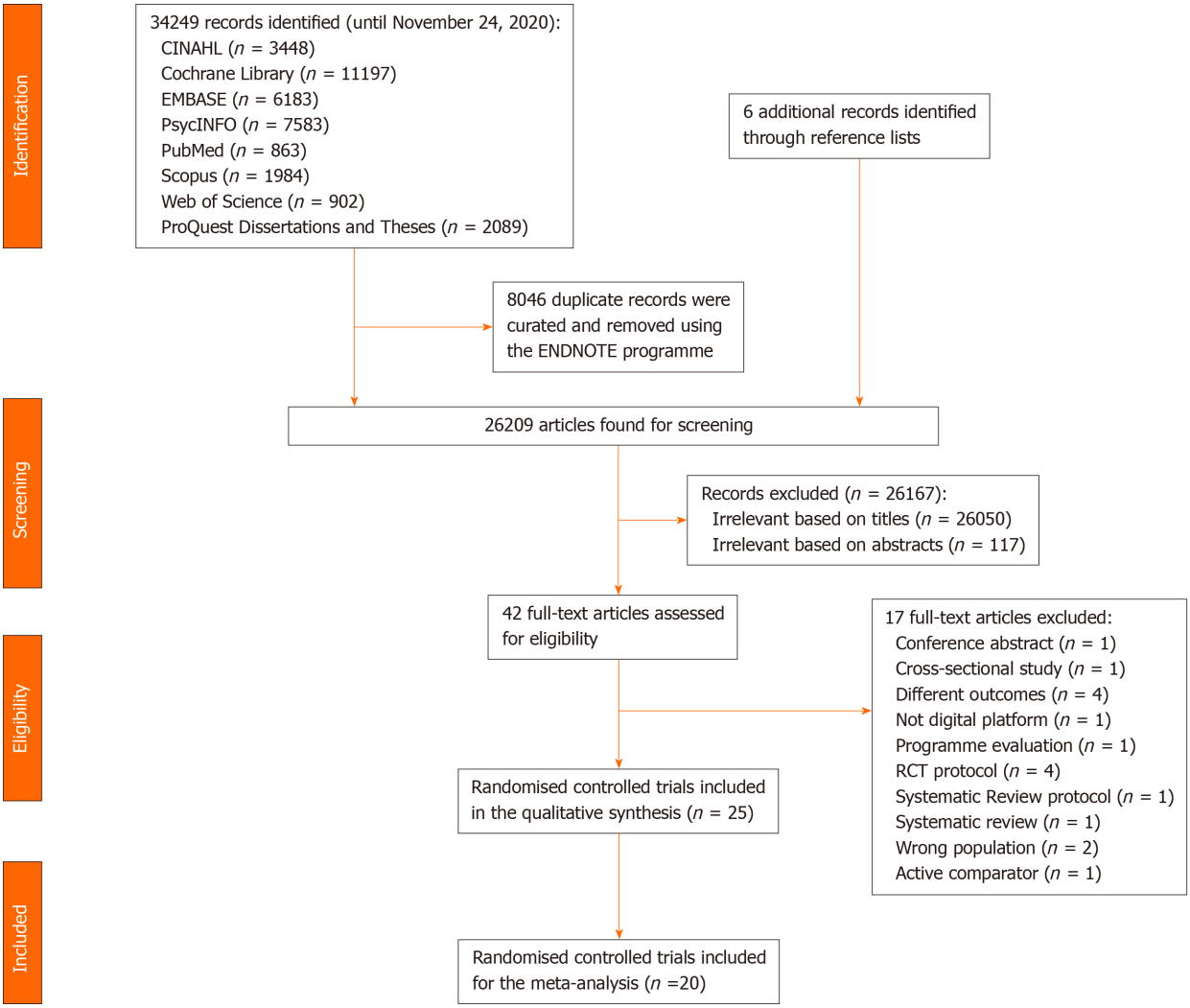


Figure 2 Study selection.

Subgroup analyses

A series of subgroup analyses was conducted (Table 2) on the basis of population nature, theoretical principle, digital platform, aim of intervention, guidance, and number of sessions. The effect sizes were greater and significant among postnatal women (g = 0.67) than antenatal women (g = 0.24). Subgroup analyses demonstrated that the essential features of the intervention, that is, the use of CBT principle only (g = 0.56) *via* a website platform (g = 0.32) for the purpose of treatment (g = 0.71) were significant. Therapist-guided intervention (g = 0.40) and ≥ eight sessions were more effective than their counterparts. However, no significant subgroup differences (P = 0.09–0.54) were found.

Meta-regression analyses

Univariate and multivariate random-effect regression was performed to examine whether the effect size magnitude was related to covariates (year of trials, age, sample size, number of sessions, type of psychotherapy, and duration of intervention), as shown in Table 3. The results of univariate and multivariate random-effect regression analyses showed that age (β = 0.18, P = 0.02; β = 0.14, P = 0.04, respectively) and the use of CBT (β = 0.07, P < 0.001; β = 0.07, P < 0.001, respectively) had significant effects on depression symptoms. The Q-value for the multivariate random-effect regression model was 68.76, with df = 16 and P < 0.001. Thus, the null hypothesis was rejected, and the effect size was related to covariates. The explained variance (R^2 = 0.364) was calculated using the regression model, and it revealed that 36.40% of the variance in true effects could be explained by these two covariates. Two bubble plots of depression symptoms on age and types of psychotherapy are presented in Supplementary Figure 2. The multivariate meta-regression model suggested that younger perinatal women who received CBT showed a larger effect size in terms of

Table 2 Subgroup analyses of digital psychotherapeutic intervention on depression symptoms

Deign	Subgroups	No of trials	Sample size	*g*	*P* value	Subgroup differences, *P* value
Population nature	Antenatal women	8[62,65,66,69,73,74,76,84]	622	-0.24	0.16	Q = 2.95, *P* = 0.09
	Postnatal women	11[67,68,70-72,75,78-81,85]	1114	-0.67	< 0.001[c]	
Theoretical principle	Cognitive behavioural therapy and others	3[67,73,78]	185	-1.11	0.19	Q = 4.13, *P* = 0.13
	Cognitive behavioural therapy only	8[62,65,69-71,79-81]	447	-0.56	< 0.001[c]	
	Other psychotherapy	8[66,68,72,74-76,84,85]	691	-0.19	0.26	
Digital platform	Website	17[64-66,68-76,78-81,85]	1538	-0.32	< 0.001[c]	Q = 2.49, *P* = 0.11
	Mobile application	2[67,84]	198	-1.93	0.06	
Aim	Prevention	9[62,68,70-74,76,85]	741	-0.25	0.09	Q = 3.31, *P* = 0.07
	Treatment	10[65-67,69,75,78-81,84]	995	-0.71	< 0.001[c]	
Guidance	Self-guided	4[65,67,73,85]	211	-0.83	0.23	Q = 0.37, *P* = 0.54
	Therapist-guided	15 [62,66,68-72,74-76,78-81,84]	1525	-0.40	< 0.001[c]	
Number of sessions	< 8 sessions	8[66,69,73,75,76,81,84,85]	650	-0.26	0.15	Q = 2.47, *P* = 0.12
	≥ 8 sessions	11 [62,65,67,68,70-72,74,78-80]	1086	-0.66	< 0.001[c]	

Hedges's *g*: Effect size; Q: Cochran's statistic; Z: z-statistics.
[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.

Table 3 Random-effects univariate and multivariate meta-regression analyses of covariates on depression symptoms

Covariates	Univariate meta-regression				Multivariate meta-regression			
	β	SE	95%CI	*P* value	*β*	SE	95%CI	*P* value
Age	0.18	0.08	0.03, 0.33	0.02[b]	0.14	0.07	0.01, 0.27	0.04[a]
Cognitive behavioral therapy[1]	-0.077	0.23	-1.23, 0.31	< 0.001[c]	-0.070	0.24	-1.16, -0.23	< 0.001[c]
Year of trials	-0.02	0.04	-0.10, 0.06	0.66	-	-	-	-
Sample size	< 0.001	< 0.001	-0.00, 0.00	0.94	-	-	-	-
Numbers of session	-0.05	0.04	-0.13, 0.03	0.20	-	-	-	-
Duration of intervention (wk)	-0.07	0.05	-0.16, 0.02	0.13	-	-	-	-

[1]Reference group: Non-cognitive behavioral therapy.
[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.
β: Coefficient; SE: Standard error; CI: Confident interval.

improving depression symptoms than older perinatal women who received other psychotherapies. However, covariates such as year of trial, sample size, number of sessions, and duration of intervention had no effect on these symptoms.

Anxiety and stress symptoms

Fourteen RCTs[65,66,70-73,75,76,78,79,81,82,84,85] assessed the effectiveness of digital psychotherapeutic intervention in 1091 perinatal women by using anxiety as an outcome. Meta-analysis results indicated that digital psychotherapeutic intervention exerted a significant effect on improving anxiety symptoms (Z = -5.72, P = 0.007), with a small effect size (g = 0.25), as shown Figure 4. Moderate heterogeneity (I^2 = 50.70%) was also found. Another 10 RCTs[70,71,73-76,78,81,82,85] used stress as an outcome in 720 perinatal

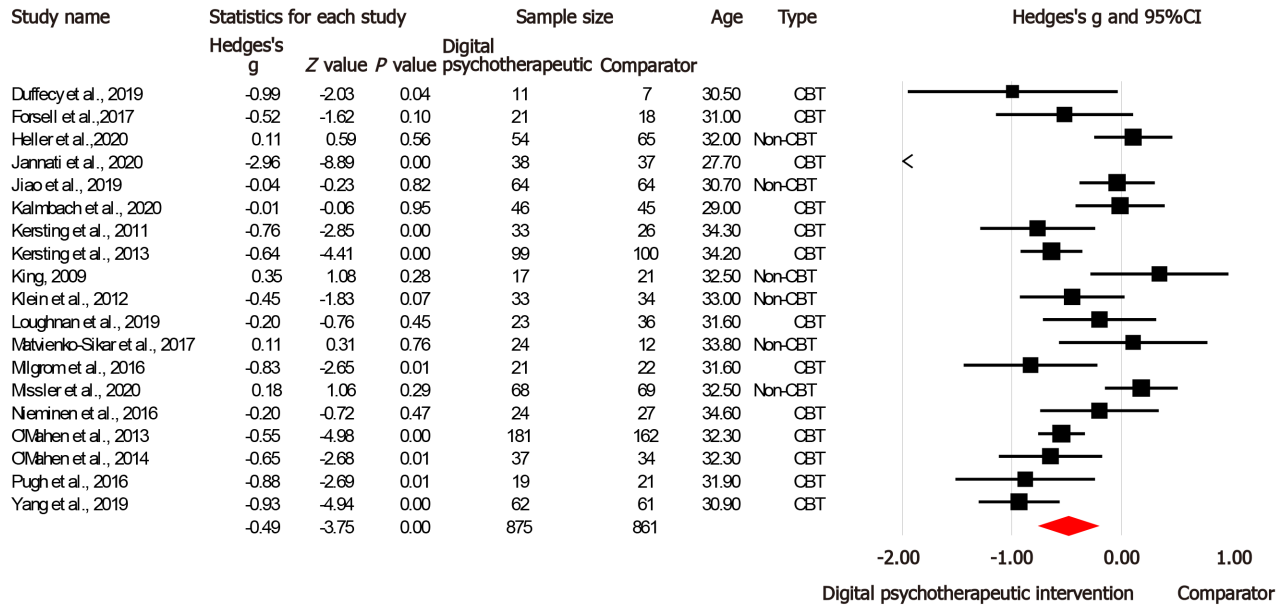


Figure 3 Forest plot of Hedges's *g* (95% confidence interval) in depression symptoms for digital psychotherapeutic intervention and comparators.

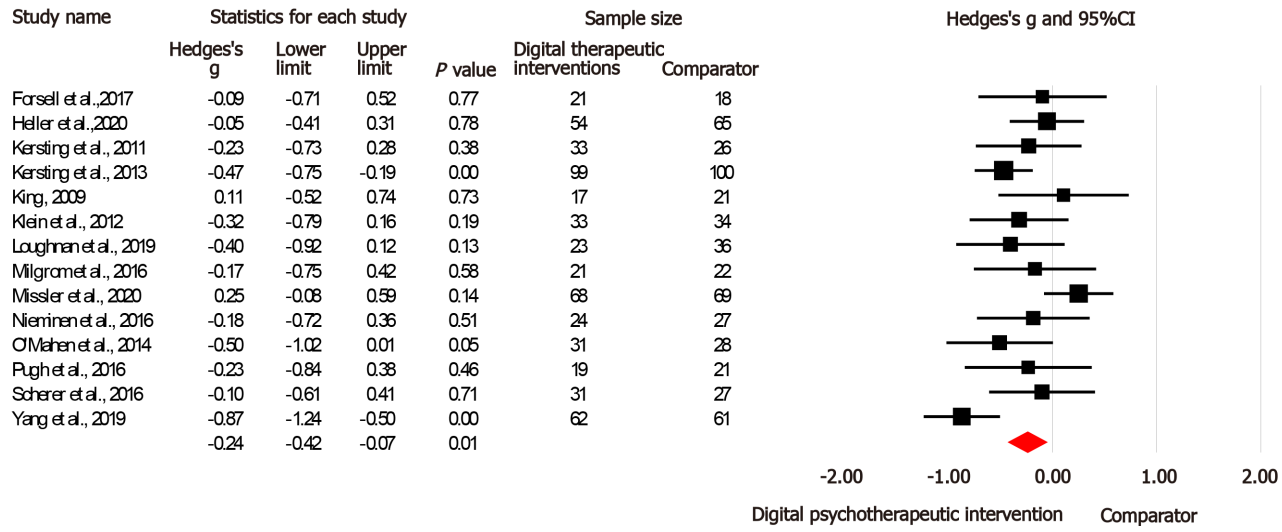


Figure 4 Forest plot of Hedges's *g* (95% confidence interval) in anxiety symptoms for digital psychotherapeutic intervention and comparators.

women. Meta-analysis results demonstrated that stress symptoms were significantly reduced (Z = -2.90, P < 0.001) in the intervention group with a medium effect size (g = 0.47) compared with the comparator (Figure 5). Considerable heterogeneity (I^2 = 75.34%) was also revealed. Sensitivity and subgroup analyses were conducted to decrease the I^2 in both outcomes, but the heterogeneity did not improve.

Narrative synthesis

Given that five trials[61,63,64,77,83] did not report inadequate data for pooling of data in the present meta-analysis, the authors were contacted three times to ask for supplementary data on the psychological outcomes. Unfortunately, the team did not receive any reply. Thus, narrative synthesis was conducted. One trial[63] showed that digital CBT considerably reduced depression and anxiety symptoms. However, one trial[62] did not clearly report psychological outcomes after intervention, and another three[61,77,83] suggested that the intervention did not significantly improve the psychological outcomes. These inconsistencies indicated the need for further investigation.

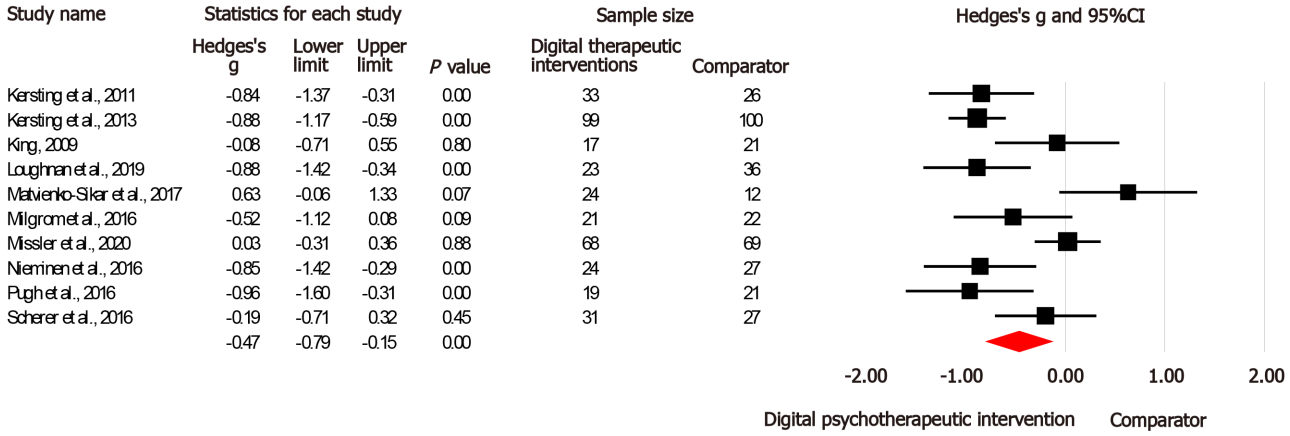


Figure 5 Forest plot of Hedges's *g* (95% confidence interval) in stress symptoms for digital psychotherapeutic intervention and comparators.

Overall evidence

In accordance with the GRADE criteria, the overall quality of evidence was graded as very low (Supplementary Figure 2). For the outcome measures of depression, anxiety, and stress symptoms, methodological limitations were downgraded because of performance, selection, and detection biases. Inconsistency was downgraded because of moderate to considerable heterogeneities (50.70%–84.41%). Indirectness was downgraded due to the variation in digital psychotherapeutic interventions. Imprecision was downgraded because of small sample size with wide confidence intervals. Publication bias was not detected for trials that reported depression, anxiety, and stress scores, as observed from the symmetrical distribution of the included trials on the funnel plots (Supplementary Table 4). The *P* value of Egger's regression asymmetry tests ranged from 0.24 to 0.33, thereby suggesting no evidence of publication bias.

DISCUSSION

This review revealed statistically significantly lower depression, anxiety, and stress symptom scores with small to medium effect in digital psychotherapeutic intervention than in the comparators. Subgroup analyses identified that the essential features of the intervention, that is a website platform with ≥ eight therapist-guided sessions using CBT principle for treatment among postnatal women appeared to be more effective in improving depression symptoms than their counterparts. Meta-regression analyses observed that the age of perinatal women and the type of psychotherapy had statistically significant effects on depression symptoms.

The findings revealed that digital psychotherapeutic interventions were effective in improving depression, anxiety, and stress symptoms among perinatal women. These results are consistent with those of previous reviews[36-38]. They could explain the proposed mechanistic pathways linking digital psychotherapeutic intervention to psychological outcomes (Figure 1). Digital psychotherapeutic interventions aid perinatal women to modify their dysfunctional thoughts[12], ameliorate their level of awareness[13], enhance their problem-solving skills[14], deal with stress[15], and acquire further knowledge[16]. Such principles of psychotherapy help build resilience, as women are able to learn and strengthen their cognitive flexibility[86]. Digital platform allows for improving connectivity, accessibility, and availability[31]. Moreover, it could reduce the time constraint, social stigma, and cost[22,32,33]. The components of digital psychotherapeutic interventions involve reminders, forums, and self-monitoring; they help enhance the ability of women to actively adapt to their circumstances and improve their abilities to cope with stressful perinatal situations[87]. As a result, perinatal women may improve their depression, anxiety and stress symptoms.

Subgroup and meta-regression analyses highlighted that the use of the CBT principle, therapist support, and ≥ eight sessions using website platform for treatment among postnatal young women could optimize the intervention effect. Efficacious intervention adopted the CBT principle, possibly because CBT is a patient-centered and personalized therapy that uses collaborative psychological approach[12]. The core

components of cognitive restructuring and behavioral activation assist perinatal women to understand their own special beliefs and behavior patterns *via* counselling, education, advice, and assignment and finding an enhanced method to modify their dysfunctional thoughts, thus bringing about emotional and behavioral changes and improving their psychological problems[12]. Therapist support involved increased levels of customized human support to provide feedback, support, questions, and answers in a flexible manner for clarifications that could intensify the effect of intervention and improve depression symptoms[88]. In addition, ≥ eight sessions was suggested to be the appropriate number for intervention. This finding seems to be a possible explanation of a dose-response effect from the cumulative intervention intensity[89].

The interventions are effective for the purpose of treatment, and they are targeted at complicated perinatal women, such as those who experienced psychological problems[65-67,73,75,78-81,84], insomnia[69], miscarriage[72], or pregnancy loss[70,71]. This finding is consistent with that of a previous review[36], which showed that preventive digital psychotherapy may not be as effective as when targeted at high-risk perinatal women. High-risk women are possibly more willing to seek help and be actively involved in psychotherapy because they felt depressed, anxious, or stressed for a long period than low-risk women[3,24].

Young women are particularly at high risk of having perinatal mental disorders because they may not access antenatal care or mental health services in a timely manner[3]. Similar to the findings of a previous review[87], interventions implemented during the postnatal period were more effective than those implemented during the antenatal period. Postnatal period is a time of adaptation to parenthood, and postnatal women need to adjust to the new role of motherhood and familial relationships[90]. Therefore, interventions were found to be more effective in postnatal women. Website was found to be the preferred platform among perinatal women. This case may be linked to perinatal women expressing interest in the use of web-based resources and their increased engagement in e-mental health[91]. One study suggested that mobile applications are an important source of support during childbearing[92]. Low statistical power in small sample size was possible because only two trials were conducted in 198 perinatal women by using mobile applications in subgroup analysis. Further investigation is necessary.

This review demonstrates that digital psychotherapeutic intervention may be a potential solution to reduce psychological problems in perinatal women. The poor quality of existing evidence reduced certainty in implementing digital psychotherapeutic intervention at this phase. However, the subgroup and meta-regression analysis results could provide a future direction in designing interventions effectively. Future designs should consider therapist-guided treatment among young postnatal women.

This systematic review has several strengths. It is the first systematic review to investigate the essential features, covariates, and quality of the overall evidence. A total of 25 RCTs were selected, and the PRISMA criteria were strictly followed, with a robust three-step search strategy throughout eight databases. RCTs were selected from over 23 countries using published and unpublished resources. Hedges's g was adopted to accurately estimate the overall effect size because of the small sample size in most of the included RCTs. However, this review also has some limitations. First, the restriction to trials in English and self-selected samples from media recruitment may have limited the generalization of the findings. Second, the high heterogeneities in the meta-analyses could have resulted from the low accuracy of pooled estimates. Third, self-report measures may have led to overestimation or underestimation of the effect size. Fourth, very low overall evidence could have diminished the internal validity of the findings. Lastly, this review only pooled post-intervention outcomes; thus, the sustainability of digital psychotherapeutic intervention remains uncertain.

This review highlighted a number of directions for future trials. Further well-designed RCTs are needed, particularly allocation concealment, participant and personnel blinding, and outcome assessment blinding. Future RCTs should stick to the consolidated standards of reporting trial statements[93]. Future trials should also consider a large sample size to provide a more precise estimate of the effect size and generalize the results. Considering that CBTs using website platform have dominated the existing literature, upcoming research should focus on different types of psychotherapy using other digital platforms for fair comparison. Future trials are warranted to assess the long-term effect and cost-effectiveness of digital psychotherapeutic intervention among perinatal women.

CONCLUSION

Meta-analyses found a small to medium and significant group difference favoring digital psychotherapeutic interventions over the comparators in regard to depression, anxiety, and stress outcomes. This systematic review provides evidence for the effectiveness of digital psychotherapeutic intervention in reducing psychological problems during the perinatal period. Future designs should consider the use of CBT principle, therapist support, and ≥ eight sessions using website platform for the treatment of postnatal young women. Further high-quality RCTs with large sample sizes are required to evaluate the sustainability of the intervention.

ARTICLE HIGHLIGHTS

Research background

Perinatal women are at increased susceptibility of psychological problems, including depression, anxiety, and stress. Perinatal psychological problems are associated with considerable adverse effects on women, offspring, family, and healthcare services.

Research motivation

Previous reviews were limited to few selected trials, a mixture of different research designs, few databases, and only narrative synthesis. None of the previous reviews investigated the preferred features of digital psychotherapeutic intervention and the influence of covariates on study effect size.

Research objectives

This review aimed to synthesize the best evidence to (1) assess the effectiveness of digital psychotherapeutic intervention in reducing depression, anxiety, and stress symptoms; and (2) evaluate the preferred design features of the intervention.

Research methods

A comprehensive three-step search strategy was conducted in congruence with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions from eight databases. Comprehensive Meta-analysis 3.0 software was used to conduct meta- and meta-regression analyses. The individual and overall quality of the evidence were evaluated using the Cochrane risk-of-bias tool and the Grading of Recommendations, Assessment, Development, and Evaluation criteria.

Research results

A total of 25 randomized controlled trials that included 3239 perinatal women were identified. Meta-analyses revealed that digital psychotherapeutic intervention significantly improved the depression (g = 0.49), anxiety (g = 0.25), and stress (g = 0.47) symptoms of perinatal women compared to the control. Subgroup analyses demonstrated that a website platform with ≥ eight therapist-guided sessions using the cognitive behavioral therapy theoretical principle was more effective than other treatments in postnatal women. Meta-regression analyses observed that the age of perinatal women and the type of psychotherapy had statistically significant effects on depression symptoms. Egger's regression asymmetry tests found no publication biases, but the overall quality of evidence was very low.

Research conclusions

This systematic review provides evidence for the effectiveness of digital psychotherapeutic intervention in reducing psychological problems during the perinatal period, particularly depression, anxiety, and stress symptoms. Future designs should consider the use of the cognitive behavioral therapy principle, therapist support, and ≥ eight sessions using a website platform for the treatment of postnatal young women.

Research perspectives

Given that the poor quality of the existing evidence reduced certainty in implementing digital psychotherapeutic intervention at this phase, further high-quality randomized controlled trials with large sample sizes are required to evaluate the sustainability of the intervention.

ACKNOWLEDGEMENTS

The authors would like to thank authors of the randomized controlled trials considered for sharing their additional data for use in our meta-analysis.

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Published by **Baishideng Publishing Group Inc**
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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 May 19; 11(5): 153-200



Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJP* as 3.545; IF without journal self cites: 3.545; Ranking: 46 among 155 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
May 19, 2021

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World Journal of Psychiatry

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World J Psychiatr 2021 May 19; 11(5): 153-168

DOI: 10.5498/wjp.v11.i5.153

ISSN 2220-3206 (online)

OPINION REVIEW

Use of cognitive event-related potentials in the management of psychiatric disorders: Towards an individual follow-up and multi-component clinical approach

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Author contributions: Campanella S is the sole author of the manuscript.

Conflict-of-interest statement: No relevant conflicts of interest to declare.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Belgium

Peer-review report's scientific quality classification

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Abstract

Relapse prevention remains a major challenge in psychiatry, thus indicating that the established treatment methods combining psychotherapy with neuropharmacological interventions are not entirely effective. In recent years, several intervention strategies have been devised that are aimed at improving psychiatric treatment by providing a complementary set of add-on tools that can be used by clinicians to improve current patient assessment. Among these, cognitive event-related potentials (ERPs) have been indexed as valuable biomarkers of the pathophysiological mechanisms of various mental illnesses. However, despite decades of research, their clinical utility is still controversial and a matter of debate. In this opinion review, I present the main arguments supporting the use of cognitive ERPs in the management of psychiatric disorders, stressing why it is currently still not the case despite the vast number of ERP studies to date. I also propose a clinically-oriented suitable way in which this technique could — in my opinion — be effectively incorporated into individual patient care by promotion of the use of individual ERP test-retest sessions and the use of a multi-component approach.

Key Words: Event-related potentials; Psychiatry; Cognitive disorders; Follow-up; Multi-component approach; Personalized medicine

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Core Tip: Despite decades of intense research and many promising results, cognitive

Grade A (Excellent): 0
Grade B (Very good): B, B, B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 22, 2021
Peer-review started: January 22, 2021
First decision: March 1, 2021
Revised: March 5, 2021
Accepted: April 14, 2021
Article in press: April 14, 2021
Published online: May 19, 2021

P-Reviewer: Akkaya C, Hosak L, Khan MM, Tcheremissine OV
S-Editor: Gao CC
L-Editor: A
P-Editor: Li JH

event-related potentials (ERPs) have yet to be implemented in daily psychiatric care units as an add-on tool to psychotherapy and medication. I present here the main arguments supporting the notion that ERPs represent a highly suitable tool for performing individual "neuro-cognitive" assessments in psychiatric patients. Such ERP data could help clinicians to specify individual cognitive interventions that will target each patient's specific needs, thus promoting an "individualized" or "personalized" medicine.

Citation: Campanella S. Use of cognitive event-related potentials in the management of psychiatric disorders: Towards an individual follow-up and multi-component clinical approach. *World J Psychiatr* 2021; 11(5): 153-168
URL: https://www.wjgnet.com/2220-3206/full/v11/i5/153.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i5.153

INTRODUCTION

The 1990s have been referred to as the "Decade of the Brain", with developments such as brain imaging tools allowing patterns of distributed neural activity associated with both normal and pathological behaviors to be identified[1]. On this basis, major mental illnesses, such as schizophrenia, autism, major depression, anxiety disorders, and addictions, were redefined as brain diseases[2], with a deep impact of the environment at both the social and physical levels[1]. Nowadays, the separation of neurology and psychiatry appears arbitrary, and in the framework of modern neuroscience, psychiatrists and neurologists could be called "clinical neuroscientists" who apply neuroscientific discoveries to the care of patients with brain disorders[3]. Clearly, the management of a mentally ill patient necessarily requires consideration (mainly through psychotherapy) of a single individual embedded in a specific social-cultural context in order to encompass the social and psychogenic aspects of individual clinical symptoms[4]. However, mapping the live brain activity of a patient, by—for instance—the use of positron emission tomography (PET), magnetic resonance imaging (MRI), or electroencephalography (EEG), has demonstrated that all normal or dysfunctional mental processes are ultimately biological[2]. It is, therefore, also important to consider these cognitive, emotional, and social processes, subtended by specific choreographed patterns of brain activity that — when dysfunctional — can mediate the onset and persistence of specific clinical symptoms[5]. For instance, an alteration of mental state attribution, the ability to infer mental states of others in order to guide social interactions, is classically observed in schizophrenic patients[6]. This deficit, mainly subtended by neural alterations in the prefrontal cortex and the superior temporal sulcus[7], is associated with a poor outcome, social functioning, and social competence in schizophrenia[8]. As antipsychotic medication has been shown to have a limited impact on recovery and social cognition[9], the challenge is to develop new therapeutic strategies to specifically improve social cognition in schizophrenia. Promising results, revealing improvement of social functioning and reduction of psychotic symptoms, have been achieved through social cognition training programs and psychosocial interventions[10] as well as by brain stimulation through transcranial direct-current stimulation (tDCS)[11] or transcranial magnetic stimulation[12]. Similarly, in major depressive disorder, deficits in cognitive inhibition, subtended by a hyperactivated amygdala insufficiently controlled by a hypoactivated prefrontal region[13] appear to be a main causal factor for ruminations[14]. Sessions of training to inhibit negative thoughts[15] as well as a combined tDCS-mindfulness program resulted in a decrease in ruminations and lower depressive scores[16], while medication only has been reported to provide modest improvements[17]. In alcohol dependence, an increased salience of alcohol-related cues grasping drinkers' attention (hyperactivated mesolimbic activity[18]) combined with a lack of inhibitory resources (anterior cingulate and frontal hypoactivity[19]) defines the main neurocognitive mechanisms triggering relapse[20]. In light of the modest effect of anti-craving medications[21], cognitive bias modification training alone[22] or combined with tDCS[23] has shown promising trend on treatment outcomes by reducing craving and by improving early abstinence. Overall, convergent empirical data illustrating alterations in brain networks that underlie cognitive impairments have provided

foundational information about transdiagnostic circuits and promising targets for intervention[24]. Indeed, numerous studies have provided consistent evidence that mental illness involves significant cognitive impairments that represent valid therapeutic targets, as enhancing cognitive functioning leads to a reduction of clinical symptoms and a better quality of life. One of the main challenges at present consists of developing new ways to use neurocognitive mechanisms as an add-on tool in the clinical and conventional management of psychiatric patients.

Due to their high anatomical resolution, PET and functional MRI (fMRI) clearly constitute the most suitable tools to assess the distributed brain networks involved in diverse cognitive functions[25]. However, their coarse temporal resolution (1-2 s) does not allow definition of the temporal activation sequence, thus preventing isolation of the series of individual sensory, cognitive, affective, and motor processes that occur between a stimulus and a response[26,27]. Electrophysiological tools, by recording spontaneous electrical brain activity from multiple electrodes placed over the scalp[28], are more suitable for this purpose due to their optimal temporal resolution on the order of milliseconds[29]. EEG is an inexpensive and non-invasive tool defining a valuable clinical first-line method to exclude a diagnosis of epilepsy, drug intoxication, or sleep disorders in psychiatric patients[30]. A derivative of the EEG technique refers to event-related potentials (ERPs), *i.e.*, averaged EEG responses that are time-locked to the cognitive processing of stimuli. The past several decades have witnessed a vast number of task-dependent ERP components being described and studied among healthy people. While studies on healthy participants have helped to define the various cognitive steps needed throughout the entire information processing stream to achieve a cognitive function, such data also have great relevance in pathology. Indeed, by accessing the various cognitive steps needed to achieve a cognitive function, cognitive ERPs may then also allow definition of where a dysfunctional behavior originates at the cognitive level. This has great clinical relevance, as a similar altered behavior may be subtended by various cognitive disorders[31]. Therefore, by indexing the specific neurocognitive functions that are dysfunctional in a patient, ERPs pinpoint cognitive functions that should be rehabilitated in each patient through specific and individualized cognitive remediation procedures[26]. However, despite a solid theoretical basis[29] and decades of research showing alterations of these components in various psychiatric diseases[32], their relevance in clinical settings is still a matter of debate[33]. The scope of this paper is not to provide an exhaustive review of the literature regarding ERPs in various psychiatric diseases. Rather, my aim is to present relevant arguments supporting the notion that it is important to incorporate the use of cognitive ERPs in the management of psychiatric disorders, by also stressing why it is still not the case nowadays despite thousands of ERP studies to date. I then propose a clinically-oriented suitable way in which this technique could—in my opinion—be effectively incorporated into individual patient care.

DECADES OF ERP STUDIES IN PSYCHIATRY: WHY SO MANY HOPES AND PROMISING RESULTS FOR SUCH A MINOR CLINICAL IMPACT TO DATE?

Depending on the cognitive task one is confronted with and the cognitive processes one is focusing on, several ERP components have been described in recent decades in the literature. The P50, the contingent negative variation (CNV), the mismatch negativity (MMN), the P300 with its P3a and P3b subcomponents, the No-go N2 and No-go P3, the error-related negativity (ERN), and the N400 are some of the most studied ERPs. When elicited through a specific task in healthy subjects, such ERPs are the neural correlates that assess the efficiency of diverse cognitive processes, such as sensory gating[34], arousal and motor preparation[35], auditory discrimination[36], novelty processing *vs* decision making[37], cognitive and motor inhibition[38], insight[39], and semantic congruency[40]. As ERP amplitudes reflect differences in the intensity of responses whereas measurements of latency inform regarding the processing time duration[40,41], several anomalies in amplitude and/or latency of these components have been reported in various psychiatric disorders[32,42]. In such a view, ERPs could characterize biological markers of pathophysiological mechanisms[43]. Such biological markers can be state (only present during the acutely ill state but stabilized after remission) or trait (always present, during and after the disease) markers[44,45]. On the one hand, by reflecting pathophysiological processes

that are active during the disease, state markers could provide clinicians important input to assist with choosing the most appropriate treatment. For instance, a decreased amplitude of the P3b component is considered to be a state marker of depression[46]: The P3b amplitude has been shown to be increased after four weeks of antidepressant treatment[47] as well as following recovery from electroconvulsive therapy[48]. Similarly, chronic schizophrenic patients exhibit reduced MMN amplitudes compared to healthy controls[49], and antipsychotics such as aripiprazole[50] or drugs acting on the NMDA (N-Methyl-D-aspartate) receptor[51] appear to induce its recovery, while the CNV is reduced in amplitude in children[52] and adults[53] with ADHD but has been shown to exhibit an amplitude recovery with even just a single dose of stimulant medication[54]. Such instances clearly highlight how ERP state markers could be particularly useful in monitoring the efficiency of a treatment. On the other hand, trait markers can also be particularly useful, mainly as indicators of vulnerability[45]. Indeed, the amplitude reduction of the P3b as well as the absence of P50 suppression in schizophrenia[55], an enhanced ERN in child and adult anxiety disorders[56], and an altered P3 component in cocaine users[57] are examples of trait markers, indexing during and after the disease, of impaired cognitive functions that play a pivotal role in the onset and persistence of these mental diseases. But importantly, such alterations can also define a risk marker for healthy people with, for instance, a positive family history to further develop it[58-60]. Therefore, such markers, if present, can improve early detection of illness, and, as such, facilitate more effective and targeted interventions[44].

Overall, state and trait ERP markers can serve to aid diagnosis (as prognostic elements[61]), assist in choosing the most appropriate treatment for psychiatric disorders[62], and help with detecting illness at an early phase[63]. However, although such empirical data, even in meta-analyses[64-68], may appear convincing and useful, the reality is quite different as, up to now, the utility of cognitive ERPs in daily clinical care settings remains (very) modest[30]. Several explanations may account for this situation. First, at a technical level, the worldwide current ERP screening procedure favours the huge number of ERP studies, despite the heterogeneity of the data. For instance, an amplitude reduction and/or a delayed latency of the P3b and the MMN is usually considered to be a state marker of depression[69] and early psychosis[70], respectively. However, contradictory data have also been reported, suggesting no P3b and MMN differences between depressive[48] and psychotic[71] patients, respectively, with controls. Such heterogeneity has understandably led to a degree of scepticism among clinicians as it raises questions regarding reliability. The main factors accounting for these discrepancies are the clinical subtypes of patients included in these studies, with comorbidities inducing particular responses[72], higher artifact contamination in clinical patients than in typical subjects[27], a potential influence of medication[27], and differences in ERP recording protocols leading to data misinterpretations[73]. In this respect, a very interesting initiative, called "ERP CORE" (Compendium of Open Resources and Experiments)[74], has recently been launched in order to provide standardized ERP paradigms for seven widely used ERP components (N170, MMN, N2pc, N400, P3, lateralized readiness potential, and ERN). By providing researchers with a useful tool and guidelines for selected tasks to record specific ERP components, this will notably promote the possibility of comparing ERP data sets from different laboratories. At a clinical level, such guidelines already exist[75]; however, their use in studies around the world is still by no means ensured, and this could notably lead to a degree of misinterpretation of the data[73]. It is, therefore, urgent to again underscore that using such guidelines accepted by the field would clearly help with clinical implementation[76] by providing access to normative data gathered on large samples in order to follow the progression of patients as a function of the treatment, but also to control for potential confounding factors, such as gender, age, medication, and comorbid symptoms. Secondly, at a conceptual level, the potential role of ERP components in the management of mental disorders has also suffered from the predominance in psychiatry of the official nosological systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD)[77]. In such a categorical view, patients either do or do not meet the criteria to be diagnosed with a mental illness, thus suggesting that the presence of a specific cluster of symptoms will necessarily correspond to a specific mental disease (*e.g.*, borderline personality disorder). On this basis, the psychiatrist will select what they consider the best option of treatment among the range of those appropriate for that specific diagnosis (*e.g.*, selective serotonin reuptake inhibitors; SSRIs). If this treatment proves to be ineffective, they will then have to choose another option (*e.g.*, combination of SSRIs and quetiapine[78]) or reconsider the former diagnosis[79]. A main and crucial point that makes this categorical approach still

dominant in psychiatry is that it greatly facilitates clinical communication among mental health practitioners, as all textbooks and practice guidelines have been developed based on these categories[80]. In such a categorical view, mental illnesses are discontinuous entities with distinct symptoms, etiologies, and biomarkers[81]. However, inter-individual variability in the severity of symptoms among patients receiving a similar diagnosis, common symptoms across different disorders, and an extremely usual comorbidity factor are well-documented facts in clinical experience[77]. In other words, common liabilities across these "categories"[81,82] are more suggestive of a dimensional underlying cross-cutting transdiagnostic structure for mental disorders[77]. This still ongoing debate regarding the transdiagnostic *vs* the categorical frameworks to guide psychopathology assessments[83] is not the scope of this paper. However, it clearly appears that, due to the dominance of the nosological approach in psychiatry, the imprecision of categorical psychiatric diagnoses[84] has been a limiting factor in understanding the pathophysiological mechanisms of human behavioral abnormalities. Indeed, although decades of research have provided evidence of the relevance of various ERP components as biological markers of mental illnesses[32,43], their clinical sensitivity has been hampered by the fact that their parameters (*e.g.*, amplitude and latency) are diagnostically unspecific[33]. In other words, ERP deficits are a common feature of several psychiatric afflictions, but they will not assist clinicians in deciding whether a given patient is depressed, paranoid, or an alcoholic (high sensitivity but low specificity). Moreover, cognition is not considered as a primary treatment target, being still envisaged as a particular category of symptoms (among others), and not as a core phenomenon triggering the onset and/or the persistence of the disease. Many psychiatrists still then focused on finding the best suited drugs combination in order to contain symptoms et minimize side effects. Therefore, the approach using ERPs to classify patients according to DSM categories was entirely inappropriate, and, in the next section, I will specify how I think ERPs may be genuinely useful in clinical settings, mainly as predictive biomarkers, *i.e.*, as measured indices that may be used to predict clinical responses to treatment[85]. Finally, at a clinical level, a major practical issue is that the majority of ERP-based studies compare their results with matched controls using grand-averaged data. While such "group results" have ample merit at a fundamental "research" level, there is now a need for more "individualized", "personalized" medicine[86], *i.e.*, individual data that helps with devising interventions that are specifically targeted based on each patient's needs[26]. In the next section, I will try to provide some insights on how ERPs may be used effectively in clinical settings as an individual monitoring tool to reveal (or not) expected changes in brain function in response to a treatment[87].

USING ERPS IN PSYCHIATRY: WHAT PERSPECTIVES?

In an influential paper published in 1991 arguing for the use of PET in clinical care[88], Wagner[88] stated that: "…Today's medical practice is yesterday's research. The bridge linking the two is technology assessment, which makes possible the acceptance or rejection of new technologies in the practice of medicine. Experience is the key determinant of effectiveness. If the information provided is not useful to the physician caring for the patient, the procedure will eventually fall by the wayside...". The notion that ERPs are useful for managing psychiatric diseases, such as, for instance, depression[89], alcohol disorders[90], or schizophrenia[91], is not novel at all. However, despite decades of research, ERPs have yet to be implemented in the clinical management of mental illnesses[27]. It clearly appears at present that the clinical value of ERP components as a diagnostic index is low[33], merely reflecting a common measure of brain dysfunction[92]. With this in mind, it is, therefore, now urgent to precisely define what constitutes be the best use of ERPs in the management of psychiatric disorders. In order words, there is a need to find out which properties of ERPs as a tool could be the best-suited ones to help with managing a currently still unsolved clinical question.

A prominent issue in the treatment of mental illnesses relates to the relapse rate[93], which is approximately 50% at 1 year and 70% at 5 years for manic episodes in bipolar disorders[94]; approximately 35% at 18 mo and 74% at 5 years following a first episode of schizophrenia[95]; and approximately 50% at 3 mo and 85% at 1 year for recently detoxified alcoholic patients[96]. Despite the beneficial impact of psychotherapy and neuropharmacological interventions, as well as the positive effect of more recent intervention strategies such as multisystemic[97], cognitive behavioral[98], or mindful-

ness[99] therapies, the relapse rate is still extraordinarily high. Clearly, the idea is not at all to discredit the existing treatment methods, but providing a complementary set of add-on tools to be used by clinicians to improve current patient assessments is still a major challenge. Starting with the fact that mental diseases are also brain disorders, a neurocognitive approach has emerged[100]. This can be summarized as follows: (1) Mental illness involves significant cognitive impairment[101]; (2) These cognitive alterations, subtended by perturbed brain networks, may trigger the onset and/or persistence of clinical symptoms, thereby defining valid therapeutic targets[24]; and (3) Retraining these cognitive functions (through the use of cognitive retraining programs and/or neuromodulation tools) has been reported to reduce clinical symptoms and to enhance patient quality of life[11,16,22,23]. Overall, once admitted to a psychiatric care unit, there is still a huge difficulty with assessing "partial recovery", which allows patients to leave the hospital to return home, and achievement of long-term "complete clinical recovery", defined as the reduction of psychiatric symptoms and functional disabilities[102].

In my opinion, it is in this regard that ERPs may have an important clinical role in the management of psychiatric patients, as a monitoring and a predictive biomarker tool. Indeed, psychiatric evaluations are made almost entirely on the basis of clinical symptoms, and the longitudinal course is determined by a clinician speaking with the patient and informants (as well as sometimes by the use of clinical scales), but diagnostic frameworks do not usually incorporate biomarkers[103]. However, once the notion that mental illnesses are subtended by impaired neural functioning is acknowledged, a main assumption is to consider that this dysfunctional brain should undergo significant and enduring neural changes in order to be reflected in medium-to-long-term real-world behavioral modifications[104]. Indeed, test-retest ERP studies on healthy participants have, for instance, shown that subjects exhibiting improvements in inhibitory performance in a Go/No-go task had a similar residual gain in inhibition one week after post-training, albeit only when this effect was neurophysiologically indexed by faster Nogo-N2 latencies[105]. Accordingly, in neuropsychiatric conditions, several studies found that specific cognitive gains induced specific brain changes that were positively associated with decreased symptoms and better quality of life, even 6 mo later[106-108]. Taking these neural modifications into account would, therefore, be of the greatest clinical relevance, as their absence would suggest a high vulnerability to relapse. In this view, state ERP markers provide the possibility (1) to monitor the change, triggered spontaneously or by a specific treatment, in neurocognitive mechanisms that are involved in the onset and maintenance of clinical symptoms in an individual patient; and (2) to verify whether these neural changes induced by the treatment are predictive of the clinical trajectory. By fostering a longitudinal follow-up and intra-individual ERP approach, recent works have tried to verify the clinical utility of such designs, in which ERP measurements are included just as one would include measurements of symptoms. In a study by our laboratory of alcohol-dependent patients undergoing a four-week detoxification program[109], we showed that monitoring the changes in dual-processes that are well-known to trigger addictions (No-go P3 for inhibition[110] and P3 for cue reactivity[111]), at the start and at the end of the program, can provide clues about the mechanisms involved in abstinence or relapse. Indeed, specific changes in cognitive ERP markers during detoxification (a preserved oddball P3 and an enhanced No-go P3) indexed complete abstinence (over a 3-mo period) in alcoholic patients. The main clinical relevance of such test-retest ERP data is the possibility of pinpointing the change in specific neurocognitive functions (cue reactivity, inhibition) during the detoxification program that can predict further abstinence. Such a procedure necessarily implied: (1) Specification of the various cognitive mechanisms that should be considered as the primary targets subtending the clinical symptoms of interest; and (2) Selection of the appropriate cognitive tasks that will generate specific and reliable ERPs related to these specific processes at an individual level.

A crucial step, therefore, concerns the identification of the various cognitive processes of interest. As such, transdiagnostic (as opposed to disorder-specific) factors appear uniquely suited to bridge psychiatric phenomena and biological substrates of behavior[77]. Transdiagnostic impairment of cognitive control[82], self-referential processes[112], working memory[113], decision making[114], and attention[115] largely contribute to the real-world socio-occupational impairment common across disorders. Decades of research have validated reliable ERP markers for such processes (No-go P3, ERN, P300, MMN, and P50, respectively). Indeed, an altered No-go P3 response inhibition, as well as a deficit in P300 (in tasks tagging updating in working memory or decision making), are neurophysiological disorders present in psychotic[116,117], bipolar[118,119], unipolar[48,120] depressive disorders as well as

in anxiety[121,122] and substance use disorders[123,124]. Studies also commonly reported an altered ERN in anxiety disorders and in obsessive-compulsive disorders[125]; an altered MMN (indexing preattentive auditory memory processing) in major depression, schizophrenia, psychosis, and substance use disorders[36]; and a deficit in P50 sensory gating in stable schizophrenic patients and euthymic bipolar patients[58]. In such a dimensional transdiagnostic view, the lack of specificity reported for these various ERP components tagging specific cognitive functions will vanish and allow monitoring of the change in these processes during a treatment, independently of a categorical disorder. Such a proposition relies on two main "technical" recommendations for future ERP screening methods: (1) The use of individual ERP test-retest sessions; and (2) The use of a multi-component approach[126].

ERP serial recordings may be used in clinical contexts for the assessment of changes in cortical function during follow-up programs[33]. Indeed, although slight differences in the wave shape, size, and timing of ERPs between individuals are usually observed, these tend to be highly stable within an individual across recordings, as high internal consistency and high test-retest reliability have been reported[127-130]. A high degree of reliability is a key factor that makes state ERP markers highly suitable for examining changes in brain activity resulting from treatment intervention or disease progression in a single patient[12]. This could provide ERPs a novel and particularly useful role in the management of psychiatric disorders. Indeed, assessing that neural changes have been induced spontaneously and/or by a treatment is a necessary outcome to envisage medium to long-term positive behavioral changes[104]. For instance, recovering a normalized MMN amplitude or P50 suppression appears to be a good indicator of abstinence in alcohol and cocaine users, respectively[131]. In such a view, it is also particularly important to always merge ERP data obtained through "active" tasks with behavioral results. To illustrate this crucial point, we can focus on contradictory data showing that excessive alcohol users compared to controls exhibited decreased No-go P3 amplitudes[38,123], probably reflecting poor neural resources indexing a poor performance; while other studies have reported increased No-go P3 amplitudes[132], probably reflecting compensatory neuro-functional mechanisms that allow drinkers to achieve a similar performance level as controls. In other words, an increased amplitude should not necessarily be interpreted as a recovered activity, and a decreased amplitude should not necessarily be interpreted as a disrupted function. Therefore, merging test-retest ERP data with behavioral performances would allow identification of patients who need to recover more neural resources to achieve better performance (*e.g.*, an increase of inhibitory No-go P3 resources to maintain abstinence in alcoholic patients[109]), while patients exhibiting compensatory or exacerbated mechanisms may need to reduce the activity allocated to the task (*e.g.*, decreased ERN in anxiety disorders to assess better emotional regulation[56]). These types of individual assessments would help clinicians specify individual interventions that will target each patient's needs, thus providing "individualized" or "personalized" medicine[26]. For instance, a recently detoxified alcoholic patient who does not exhibit improvements on the No-go P3 component could be redirected to post-cure specific inhibitory boosting programs[109], while a patient with a severe anxiety disorder who does not exhibit a reduced ERN due to a drug treatment could be directed to therapies that address emotional regulation such as mindfulness[133]. Naturally, it is important at this point to outline that, on the basis of DSM or ICD psychiatric categories, some ERP trait markers have also been described. For instance, obsessive-compulsive disorder has been characterized by an increased ERN both before and after therapy[68] as well as for the altered P3 component in cocaine users[57]: Such trait markers, *i.e.*, neurophysiological mechanisms persisting during and after the disease, suggest that such ERP markers could be related to the risk for the disorder but not the expression of its phenotype. Even in a dimensional perspective, such trait markers, if present, can improve early detection of illness (*e.g.*, in healthy people with a positive family history), and, as such, facilitate more effective and targeted interventions[44]. Moreover, this also highlights a main challenge of future "ERP research applied to the clinic" to develop novel interventions/manipulations that could modify an ERP of interest. As such, it was found for instance that performing a secondary dual-task resulted in a reduced ERN, and this reduction was larger in patients with obsessive-compulsive disorder than in the group of healthy participants[134], as well as a single session of attention bias modification[135] or expressive writing[136], thus suggesting that increased ERNs in clinical anxiety disorders can be normalized, at least temporarily[137]. Increased sensitivity of the P3a and the P3b amplitudes to depression severity are also now observable thanks to the development of adapted new ERP protocols, such as the three-stimulus oddball design[138,139] and bimodal

oddball protocols[140,141], respectively. Research assessing the efficiency of a procedure or a treatment to impact an ERP of interest, even in healthy participants, will, therefore, remain of fundamental relevance in the ERP research area.

Many ERP studies have focused on "a single ERP component" (*i.e.*, P50, MMN, P3a, P3b, *etc.*), comparing it in a pathological population *vs* healthy matched control. However, at the clinical level, it has been suggested that although ERPs clearly exhibit high sensitivity and predictive power, they suffer from poor specificity[26,33]. The idea that a "multivariate endophenotype", based on a weighted combination of diverse electrophysiological features, may provide more information than any single endophenotype, is not novel[142]. Price and colleagues compared and contrasted four electrophysiological endophenotypes — MMN, P50, P300, and antisaccades — and showed that this combination of features decreased the impact of group heterogeneity. In the same vein, at an individual level, a prominent idea is that a psychiatric patient will exhibit various cognitive disorders, of varying severities, that will subtend their own clinical symptoms. In a dimensional view, such disturbances may evolve differentially, so that some ERP measurements that index a specific cognitive function may recover during a disorder, while others will exhibit long-lasting damage. As an example, we recently showed that a post-cure 3-mo abstinence period in alcoholic patients can be neurophysiologically indexed by an increased No-go P3 yet similar oddball P3 components between the start and the end of a detoxification program[109]. Future studies should hence adopt a multi-component approach in order to potentially increase the sensitivity of ERP recordings, as the change in the patterns of ERPs could be specific (*e.g.*, which components recover, and which remain disturbed) from one psychiatric patient to another. In my opinion, such patterns indexing the changes of various ERP components through test-retest sessions appear to be the best way for ERPs to provide clinicians with relevant information regarding change in the disease (due to a treatment) in a single patient and the residual cognitive impairments that still need to be addressed. Indeed, once cognitive disturbances have been characterized through ERP screening of individual patients, psychiatrists will be able to orient the "cognitive" treatment (individually or in groups that present homogeneous patterns of cognitive deficits). More precisely, specific cognitive retraining procedures could be used to target deficits and to increase cognitive efficiency, as both cognitive training and neuromodulation boosting methods have already been shown to reduce clinical symptoms[143,144].

CONCLUSION

The main aim of this opinion review was to present the main arguments in favour of the clinical utility of ERP components to help in the management of psychiatric disorders. ERPs may be of great value to psychiatrists for the identification and monitoring of cognitive processes that should be rehabilitated on a patient-by-patient basis[126]. Such a proposition is limited per se, as, naturally, the complexity of dealing with a mental illness encompasses a large variety of stakeholders, such as psychologists, psychiatrists, nurses, and social workers, as well as neuropsychologists and neurophysiologists. I am, therefore, fully aware that the ERP contribution would be minimal, as moreover, many other EEG tools (*e.g.*, event-related oscillations[145] or microstates[146]) could also be of interest. Also, combining ERPs data with more structural and functional information (through for instance fMRI studies[147,148]) would be of the greatest relevance in order to better capture the pathophysiological mechanisms underlying specific clinical symptoms and orient treatment. I am also fully aware that there is still a long way to go before such a proposition could be widely implemented in clinical care units: If such a procedure could be quite easy to install at a technical level for inpatients in psychiatric clinics in highly developed countries, the situation could be more problematic for lower-income countries, and even more for outpatients visiting on a punctual daily basis a psychiatric office. If such a procedure would reveal high efficiency in the future, economical discussions will have to be undertaken to furnish full access of such a material to all countries in order to (1) manage, monitor and orient treatment for inpatients; and (2) allow straight collaborations between research centers and outpatients' psychiatric office in order to deliver information to clinicians that could be of help in orienting treatment. In such a view, lack of normative data, technical artefacts linked to the recordings with patients, adoption of clear multisite guidelines, as well as a constructive dialogue between researchers and clinicians in the assessment of a suitable cognitive-ERP battery are still some of the main issues that warrant our full attention. A major issue with such a

proposal indeed relates to the fact that clinicians and researchers have to agree on a cognitive ERP-battery that could be used across centres (in terms of its content, but also, naturally, its multisite technical guidelines) and across disorders. Such a battery should be as complete as possible, but not too time-consuming in order for it to be adapted to all types of psychiatric patients (probably approximately a maximum of 45 min for a session recording?). It is nowadays well-accepted that transdiagnostic impairment of cognitive control[83], self-referential processes[112], working memory[113], decision making[114], and attention[115] largely contribute to the real-world socio-occupational impairment common across disorders. Therefore, I am inclined to suggest that such a cognitive ERP-battery should at least include two active and two passive tasks: (1) A Go/No-go task, which appears to be the best-suited task to assess cognitive control[143], and to record the No-go N2, the No-go P3, and the ERN as the main ERPs of interest; (2) A bimodal (visual-auditory) three-stimulus oddball task, in order to probe for updating memory and decision-making processes through the recording of P3a and P3b components[87,140]; (3) A passive auditory paired-stimulus paradigm, classically used to record sensory gating through the P50[149]; and (4) A passive auditory oddball design in order to access the MMN component[150]. Monitoring the changes in these components in a single patient during treatment would be of the greatest clinical interest for identifying neural changes that are positive predictors of the clinical trajectory as well as cognitive functions that still warrant being trained. Clearly, much work is still needed to achieve this aim, such as reaching an agreement regarding the battery content as well as establishing multicenter large sample recordings to obtain normative data and to test the efficiency of the procedure at a clinical level. Nevertheless, as EEG is a cheap method that can be readily implemented in any type of psychiatric care unit, and because ERPs can provide invaluable information regarding the neurocognitive status of a patient as a monitoring and a predictive biomarker tool, I very much think this method deserves attention and should be given more consideration for further development. The challenge for future studies will be to establish whether this procedure, driven by serial follow-up recordings of various ERP components in a singular patient, is efficient enough to be incorporated into novel psychiatric treatment methods.

ACKNOWLEDGEMENTS

I thank the Belgian Fund for Scientific Research (F.N.R.S., Belgium) and the Brugmann Foundation (CHU Brugmann, Brussels, Belgium). A special thanks also to all collaborators of my EEG team (Kajosch H, Hanard F, Schroder E, Dousset C and Ingels A), to Guérit JM and Debatisse D who were my mentors in using ERPs, and to Boutros N and Otte G for their support on this topic.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 May 19; 11(5): 169-180

DOI: 10.5498/wjp.v11.i5.169

ISSN 2220-3206 (online)

OPINION REVIEW

Implications from translational cross-validation of clinical assessment tools for diagnosis and treatment in psychiatry

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Author contributions: Stoyanov D contributed conceptualization; Aryutova K and Paunova R wrote the original draft; Kandilarova S and Todeva-Radneva A reviewed and edited the manuscript; Paunova R contributed visualization; Kandilarova S contributed supervision; all authors have read and agreed to the published version of the manuscript.

Conflict-of-interest statement: None to be declared.

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Abstract

Traditional therapeutic methods in psychiatry, such as psychopharmacology and psychotherapy help many people suffering from mental disorders, but in the long-term prove to be effective in a relatively small proportion of those affected. Therapeutically, resistant forms of mental disorders such as schizophrenia, major depressive disorder, and bipolar disorder lead to persistent distress and dysfunction in personal, social, and professional aspects. In an effort to address these problems, the translational approach in neuroscience has initiated the inclusion of novel or modified unconventional diagnostic and therapeutic techniques with promising results. For instance, neuroimaging data sets from multiple modalities provide insight into the nature of pathophysiological mechanisms such as disruptions of connectivity, integration, and segregation of neural networks, focusing on the treatment of mental disorders through instrumental biomedical methods such as electro-convulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS). These methodologies have yielded promising results that have yet to be understood and improved to enhance the prognosis of the severe and persistent psychotic and affective disorders. The current review is focused on the translational approach in the management of schizophrenia and mood disorders, as well as the adaptation of new transdisciplinary diagnostic tools such as neuroimaging with concurrently administered psychopathological questionnaires and integration of the results into the therapeutic framework using various advanced instrumental biomedical tools such as ECT, TMS, tDCS and DBS.

Key Words: Translational neuroscience; Evidence-based psychiatry; Schizophrenia; Affective disorders; Psychopharmacology; Electro-convulsive therapy; Transcranial magnetic stimulation; Transcranial direct current stimulation; Deep brain stimulation

s/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Bulgaria

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 19, 2021
Peer-review started: February 19, 2021
First decision: March 16, 2021
Revised: March 17, 2021
Accepted: March 31, 2021
Article in press: March 31, 2021
Published online: May 19, 2021

P-Reviewer: Kotzalidis GD
S-Editor: Gao CC
L-Editor: Webster JR
P-Editor: Li JH

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Core Tip: The current review is focused on the translational approach in the management of schizophrenia and mood disorders, as well as the adaptation of new transdisciplinary diagnostic tools such as neuroimaging with concurrently administered psychopathological questionnaires and integration of the results into the therapeutic framework using various advanced instrumental biomedical tools such as electro-convulsive therapy, transcranial magnetic stimulation, transcranial direct current stimulation and deep brain stimulation.

Citation: Aryutova K, Paunova R, Kandilarova S, Todeva-Radneva A, Stoyanov D. Implications from translational cross-validation of clinical assessment tools for diagnosis and treatment in psychiatry. *World J Psychiatr* 2021; 11(5): 169-180
URL: https://www.wjgnet.com/2220-3206/full/v11/i5/169.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i5.169

INTRODUCTION

Behavioral disorders are amongst the leading causes of disability and their characteristic features including early age of onset as well as high prevalence among the working-age population are an influential determinant of their negative socio-economic impact[1,2]. The severe mental illnesses, such as schizophrenia and mood disorders demonstrate a high comorbidity rate with somatic diseases as well as with other psychiatric conditions, which in addition to the significant risk for self-inflicted death, marks a high mortality rate[3].

Unlike other branches of medicine, where the clinician can rely on objective measures (blood tests, imaging methods, *etc.*), in psychiatry, diagnosis is mediated by subjectivism, which affects the reliability of the assessment methods used. Consequently, there is a frequent change in psychotropic drugs which leads to increased risk of drug-resistant disorders and relapse[4]. The integration of neuroimaging evidence with comprehension of the role of brain networks and their abnormal interactions as a pathogenic mechanism for the development of certain behavioral deviance is an important step toward a systematic biological understanding of mental disorders.

Establishing a diagnosis and treating these disorders is challenging. Numerous molecules are assumed to have the appropriate characteristics to induce improvement; however, therapeutic outcome and adverse side effects differ significantly among patients[5]. With conventional treatments (psychopharmacology and psychotherapy), a large percentage of patients report inadequate symptom resolution, and relapse rates remain high[6,7]. A growing amount of interest has been centered on focal neuromodulation in the search for better treatments. The interest in this field is driven by the latest data considering neuroanatomical models of modulation of mood, thought, perception, and behavior, as well as more sophisticated techniques for direct and focal modification of the neural function.

In the current review we will discuss new perspectives of the translational approach in the diagnosis and treatment of severe mental disorders, namely schizophrenia and mood disorders. Although genetic risk factors and pharmacogenomics in the field of psychiatry are promising strategies to predict or mitigate the therapeutic response of medication, and thus to inform medication selection and dosing decisions, the focus in this review will be on the adaptation of new transdisciplinary diagnostic methods such as neuroimaging and concurrently administered psychopathological questionnaires and the implementation of the results into treatment using various advanced biomedical treatment methods like electro-convulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS).

PSYCHIATRIC DIAGNOSTICS IN THE 21ST CENTURY

One of the most widely discussed problems in psychiatry seems to be the fact that the diagnostic process is primarily focused on patients' reports, behavioral observation and the capacity to draw conclusions about the real inner nature of patients' experiences, rather than on accurate objective biomarkers[8].

The primary diagnostic tools in contemporary psychiatry are the International Classification of Diseases[9] and the Diagnostic and Statistical Manual of Mental Disorders[10], yet their foundational criterial categorization lacks biological validity[11,12]. This phenomenon is illustrated by existing barriers, such as heterogeneity, comorbidity, and ambiguous distinctions between healthy and abnormal behavior, which impede the diagnostic process. Another significant concern is that mental illnesses are categorized purely on clinical manifestations, without consideration for their etiology. When the conventional diagnostic labels themselves are not absolutely accurate, it is difficult to recognize a biological marker for a specific disorder. For this purpose, the National Institute of Mental Health has introduced the Research Domain Criteria Project[13,14], which seeks to extend the understanding of brain-behavior correlations and eventually incorporate this knowledge into clinical practice and enhance the development of more successful treatments. Innovative brain imaging technology provides the possibility to discover disease-specific anatomical and functional neural impairments.

Neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography, single-photon emission computed tomography, magnetoencephalography and electroencephalography provide resources for a non-invasive analysis of the brain structure and function associated with mental diseases with excellent precision[15]. Understanding the complex mechanisms of communication between different brain regions at rest and in the conditional performance of tasks is a promising field for studying the etiological mechanisms of severe mental illnesses that lead to personal and social decline. For example, functional MRI (fMRI) used in schizophrenia research was able to detect anatomical and functional aberrations of brain plasticity and connectivity, which clinically manifest as cognitive disturbances[16]. Another example of an accessible translational method is pharmacological fMRI[17], which facilitates the study of the effects of different pharmacological agents on the central nervous system (CNS) and the search for accurate neuroimaging biomarkers[18].

TRANSLATIONAL APPROACH

The concept of translation can be defined as a mechanism for improving health status, thus reducing mortality and morbidity rates among patients by incorporating scientific findings from research into clinical applications[19]. The translational approach in psychiatry encompasses a wide range of scientific disciplines and innovative techniques. MRI techniques such as quantitative structural imaging, voxel-based neuromorphometry, functional neuroimaging and spectroscopy are widely used in psychiatric research. These imaging tools, together with the knowledge gained regarding the underlying neurochemical dysfunctions have the potential to change the current state of "crisis" in psychiatry[20,21] through the use of evidence-based biomarkers and insight into the etiology of mental disorders.

Disruptions in communication within and between brain networks and the pathological processes involving their nodes are a promising discovery of translational neuroscience towards gaining a biological understanding of mental disorders and defining them as impaired connectivity disorders. Low-frequency variations in random brain functions can be localized by resting state fMRI (rs-fMRI), representing a common instrument for macro-scale functional connectomics to characterize inter-individual discrepancies in brain activity and mind-brain interactions observed in various mental disorders[22]. These metrics have a tremendous potential for accelerating the discovery of biomarkers for different mental disorders, which need first and foremost reliability and reproducibility to be addressed.

In this sense, critical questions are whether the progress in this field has succeeded in contributing to the development of more effective therapeutic methods, and whether biomarkers could be incorporated into everyday practice. However, despite years of efforts in this area, the results remain inconsistent[23]. Over the past decades, substantial advancement has been made in recognizing and understanding the fundamental neurobiological correlations of psychiatric disorders, such as schizo-

phrenia spectrum disorders and mood disorders, but the effects of these advancements have not yet been established in clinical practice[24-26]. This may be partly due to the specificity of the design of the methods used. A common practice in fMRI studies is to conduct a clinical assessment before and after the scanning. Yet, in cases such as examining patients with bipolar disorder with rapid cycling, which presents with mood shifts from depression to mania within hours for example, this could affect the accuracy of the findings. To address this issue, fMRI gathered neuroimaging data, together with the parallel implementation of a self-assessment scale[27], could construct a scientifically valid instrument that can be used by clinicians in daily practice with trust in the reliability of the method. This initiative might positively affect the diagnostics, prevention, treatment, as well as facilitate the decision regarding the choice of the appropriate therapeutic method.

With the aim of implementing the translational model in psychiatry, our research group is concentrating on developing a new paradigm that combines a clinical self-assessment scale (von Zerssen and Koeller[28]'s paranoid-depressive scale) applied simultaneously with the acquisition of fMRI in two groups of patients—with a paranoid syndrome in the context of schizophrenia and with a depressive syndrome in the context of recurrent depressive disorder or bipolar disorder[29-33]. The goal is to compare the differences in brain activation during the task-related fMRI (tr-fMRI) with structural and functional changes in connectivity at rest with the hypothesis that the zones which demonstrate differential activation may have aberrant effective connectivity patterns and structural abnormalities. The results of the study can be summarized as follows: (1) In terms of grey matter (GM) volume alterations, the comparison at a whole brain level, voxel by voxel, yielded no significant structural differences between the two groups; (2) The paranoid group was associated with significantly more robust activations in the default mode network (DMN) structures—left precuneus (PreCu), left posterior cingulate cortex (PCC), and angular gyrus (AngG) during the processing of paranoid items from the scale (Figure 1); and (3) There was an aberrant connectivity pattern in the paranoid group—abnormal inhibitory connection from the prefrontal cortex (PFC) to the anterior insula (aI) (Figure 2).

We suggest that the observed activations of the PreCu, PCC, and AngG (DMN components) may be indirect evidence of the inhibitory influence from PFC⇒aI, which interferes with the balancing function of the insula as a dynamic switch in the DMN and fronto-parietal network (FPN)[32]. Impaired aI⇒DMN and aI⇒FPN connections lead to hyperactivity of DMN[34], which could explain social withdrawal and autistic behavior observed in patients with schizophrenia. In addition, the identified inhibitory effective connectivity from PFC⇒aI offers new insights into how the PFC dysfunction may contribute to cognitive impairment[35-37], behavioral disorganization[38], and functional decline observed in patients with schizophrenia. We propose a pathophysiological model in which cognitive deficits are due to the inability of the CNS to initiate and maintain an organized fronto-insular network[36].

On the other hand, we raise the question of whether and to what extent the prediction of clinical diagnostic classes can be improved by superimposing different dimensions of MRI (structural, tr-fMRI and rs-fMRI) compared to a single modality by application of a multivariate linear model (MLM)[36]. Using MLM and principal component analysis, we have made progress towards distinguishing the two psychiatric populations. The dopamine-ergic and noradrenaline-ergic pathways with DMN nodes were reported to be significant. The regions involved [planum polare (PP), inferior frontal gyrus (IFG), insula, nucleus accumbens, *etc.*] have both structural and functional characteristics that can distinguish the two groups. When focusing on the discriminatory power of the functional modalities, the predominant regions are a part of the effort mode network, DMN, and subcortical areas with mainly glutamate-ergic and GABA-ergic neurotransmission. The most significant structure in our MLM study is PP, which is a part of the superior temporal gyrus (STG) and is not only involved in auditory and linguistic processing but is also a critical construct for cognitive processes. Neuroimaging studies show that subjects with schizophrenia have structural abnormalities in the STG[39], suggesting that it plays a key role in the etiology of auditory perceptual disturbances and disorganization of thoughts[40]. There is evidence that auditory hallucinations are associated with a functional network of brain areas, namely the auditory and linguistic areas of the STG and IPG, as well as speech motor areas in the IFG[41-43], which are also significant regions in our study. Those findings support the abovementioned aim to develop a translationally valid instrument in the diagnostic process of schizophrenia and depression.

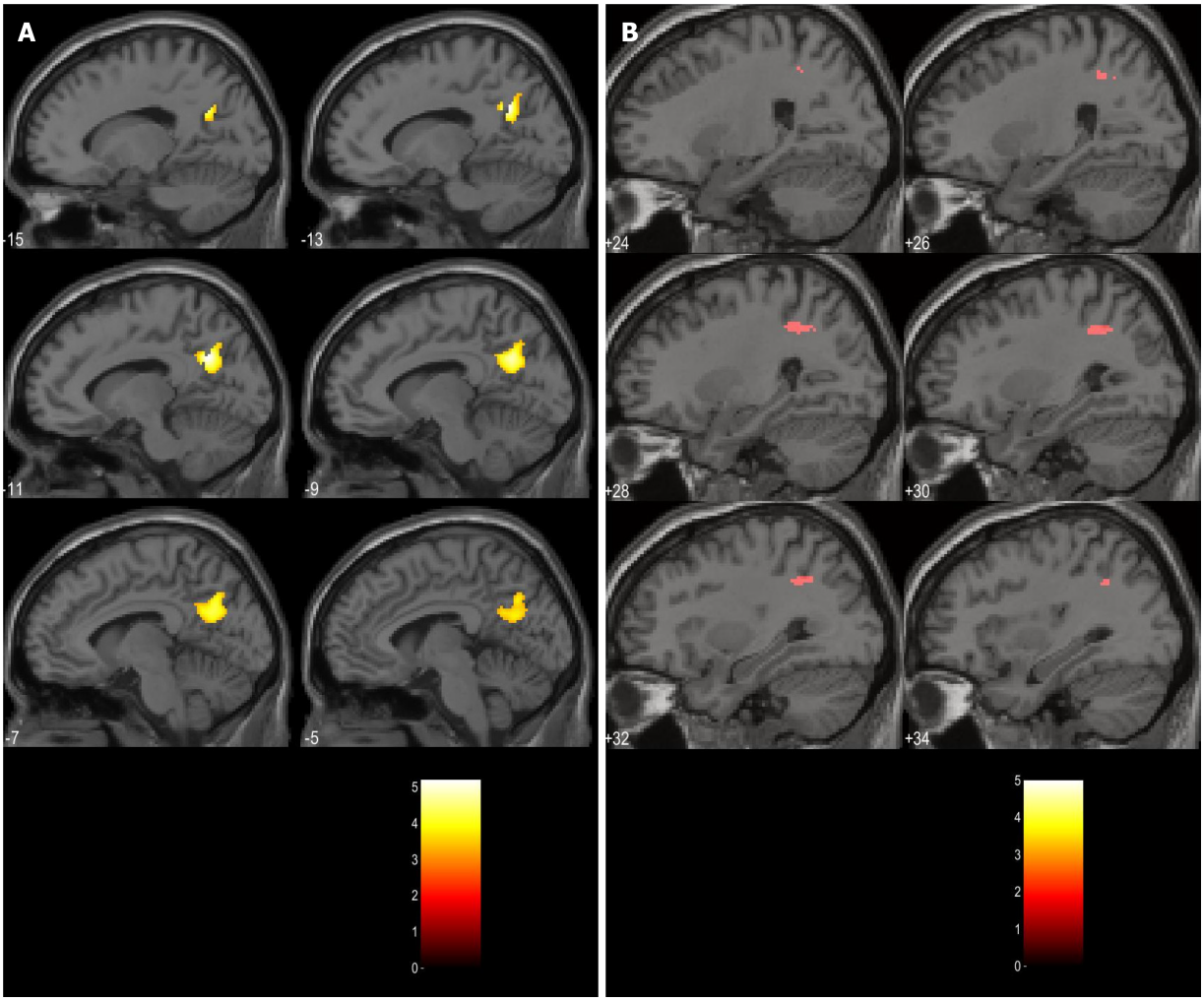


Figure 1 Clusters of activations significantly higher in schizophrenia. A: Left precuneus; B: Right posterior parietal lobule. Citation: Stoyanov D, Aryutova K, Kandilarova S, Paunova R, Arabadzhiev Z, Todeva-Radneva A, Kostianev S, Borgwardt S. Diagnostic Task Specific Activations in Functional MRI and Aberrant Connectivity of Insula with Middle Frontal Gyrus Can Inform the Differential Diagnosis of Psychosis. *Diagnostics (Basel)* 2021; 11(1): 95. Copyright ©The Author(s) 2021. Published by MDPI[32].

TREATMENT IMPLICATION OF THE TRANSLATIONAL APPROACH

Considering the controversial efficacy of the conventional treatments (psychopharmacology and psychotherapy), a large percentage of patients do not achieve complete remission (*i.e.*, become asymptomatic) or retain symptomatic improvement. This lack of efficacy has led to the quest for alternative solutions, which involve the utilization of more invasive interventions for treatment-resistant patients with psychiatric illnesses[44]. Therefore, the focus has been on neuromodulation, *i.e.*, modulation of the connections between various pathways and neurotransmitter systems in the brain. This emphasis has been driven by enhanced neuroanatomical concepts of mood, thought, and behavioral control, as well as more techniques to modify neural activity directly and focally.

ECT

ECT was first performed by a team of physicians led by Ugo Cerletti and Lucio Bini in 1938[45,46], along with Accornero[47] who contributed to the development of what they called electroshock[48] leading to the replacement of less effective biological interventions such as deep sleep therapy[49] and insulin shock therapy[50]. ECT has come a long way in refining the method and is still used today in cases of severe major depressive disorder (MDD), mania, and catatonia as a safe and effective treatment, despite the numerous critiques. ECT is an ideal example of translational neuroscience, involving the application of an instrumental method that generates electricity acting at a neurobiological level and modulating neuronal plasticity and brain connectivity. In the macro- and micro-environment of the brain, ECT induces numerous

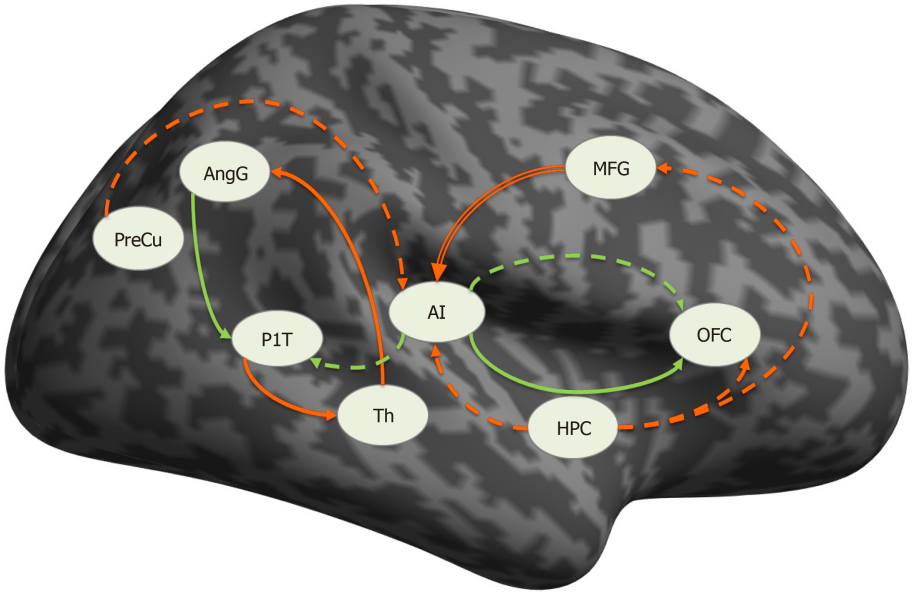


Figure 2 Connections significantly different from zero. Solid line: schizophrenia, dashed line: in depression, green: excitatory, red: inhibitory, double red line: significantly different between the groups. PreCu: Precuneus; HPC: Hippocampus; AI: Anterior insula; AngG: Angular gyrus; OFC: Orbitofrontal cortex; PIT: Planum temporale; Th: Thalamus; MFG: Middle frontal gyrus. Citation: Stoyanov D, Aryutova K, Kandilarova S, Paunova R, Arabadzhiev Z, Todeva-Radneva A, Kostianev S, Borgwardt S. Diagnostic Task Specific Activations in Functional MRI and Aberrant Connectivity of Insula with Middle Frontal Gyrus Can Inform the Differential Diagnosis of Psychosis. *Diagnostics (Basel)* 2021; 11(1): 95. Copyright ©The Author(s) 2021. Published by MDPI[32].

neurophysiological as well as neurochemical changes. It has been suggested that changes in gene expression, functional connectivity, neurotransmission, membrane permeability, and immune system function are responsible for the therapeutic effects of ECT[51]. Neuroimaging studies show that the GM volume of key regions like the amygdala, hippocampus, and anterior cingulate cortex (ACC) is decreased in patients with depression and increases following administration of ECT[52]. It remains an unresolved issue as to whether ECT efficacy in various psychiatric conditions (depression, mania, catatonia, delirium, and psychosis) is due to common neurobiological features shared by those disorders or to a single mechanism of action[53]. A mechanism that has recently been suggested is that the seizures triggered by ECT may induce a significant alteration in the sleep structure[54].

We suggest that this and other hypotheses concerning neuroplasticity can be tested by our paradigm as it can be used as a tool to monitor the therapeutic effect of ECT by comparing the results before and after the procedure, considering the fact that the von Zerssen and Koeller[28]'s self-assessment scale was primarily designed for monitoring the treatment response.

TMS

TMS was developed in 1985 as a non-invasive method to stimulate the cerebral cortex[55]. A strong magnetic field is produced by a TMS device, which induces an electrical current in a specific area. This is a method based on the principle of electromagnetic induction, which can have a different effect on the targeted areas depending on the stimulation parameters and the physiological activity of the areas. Low frequencies around and below 1 Hz (low frequency TMS) have been found to suppress the excitability of the stimulated cortical zone and functionally related structures, while those above 1-3 Hz (high frequency TMS) lead to its activation[56].

Unlike ECT, the administration of TMS requires no anesthesia and therefore patients are awake and alert during the procedure and it is often performed in an outpatient setting[57]. The short-term effect of the procedure is prolonged by applying a series of stimuli with a certain frequency, the so-called repetitive TMS (rTMS). TMS affects the underlying brain structures by altering the regional activity in the underlying cortical structures. Such changes have also been found in brain areas distant from the site of stimulation, proving that the effect of rTMS propagates in other remote parts of the brain, and these changes are functionally significant and take place on existing neural networks[58].

Depressive disorders are the most studied area of therapeutic use of TMS. Recently there has been an increasing interest in the management of schizophrenia as research results indicate that the negative symptoms of schizophrenia appear to be attributed to PFC hypoactivity, whereas positive symptoms appear to be correlated with left temporo-parietal cortex hyperactivity[59]. It has also been hypothesized that auditory hallucinations may be attributed to aberrant activation of language perception zones (*i.e.*, Wernicke's area) in the left temporo-parietal cortex[60]. It is therefore proposed that the use of high frequency TMS in the left PFC may reduce negative symptoms of schizophrenia, whereas the application of low-frequency TMS to the left temporo-parietal cortex may reduce the positive symptoms[60,61].

Considering the fact that all of those structures appear to be significant in our MLM study, we support the abovementioned model for applying rTMS in individuals suffering from schizophrenia. Moreover, our finding of the effective connectivity aberration between the PFC and the insula provides further insight on the etiopathophysiology of schizophrenia and the role of the disruption of the salience and executive systems processing due to the insular dysfunction because of its failure as a dynamic switch between the DMN, FPN and salience network (SN). Due to its deep location, the insula is considered to be beyond the reach of rTMS. However, we suggest that the insula may still be indirectly modulated by the identified abnormal connectivity from PFC to aI by focusing on PFC, the localization of which makes it accessible for stimulation.

Despite the promising applications of TMS, in about 30% of cases the standard procedure misses the target area, as it only allows stimulation of focal areas just below the skull[62,63]. Deep TMS (dTMS) has been implemented to overcome these drawbacks. dTMS offers all the advantages of conventional TMS with the benefit of stimulating deeper brain zones with lower focal distribution of the electric field[64]. Some studies have been conducted on the use of conventional TMS for the treatment of auditory hallucinations in drug-resistant patients with schizophrenia, which have shown that the method is moderately effective[65,66]. In this sense, we propose inhibitory dTMS as a therapeutic intervention targeting temporal, frontal, and parietal areas, taking into account data from functional neuroimaging which established that hallucinations are accompanied by transient hyperactivity in specific zones—STG, PFC, ACC, inferior parietal cortex, *etc.*[67] and dTMS may be even more effective than conventional TMS due to greater stimulus depth. In addition, dTMS can even be used as a method to modulate the function of the insula directly, unlike standard TMS, in which this area is inaccessible and can only be reached indirectly. Restoring the function of the insula and the networks in which it participates will further improve the function of the SN as a dynamic switch between DMN and FPN. Finally, our paradigm in tr-fMRI can also be applied as a tool for monitoring TMS, with good enough accuracy and reliability of the method.

tDCS

TDCS is a neuromodulatory procedure that facilitates or inhibits spontaneous neuronal activity by delivering low-intensity direct current to cortical areas *via* scalp electrodes. Over the past decade, the physiological mechanisms of action of tDCS have been studied to support the investigation of its clinical neuropsychiatry applications. TDCS was developed as a treatment method for brain injuries and neuropsychiatric disorders, especially MDD. Given the absence of a triggered seizure, it is hypothesized that this technique operates by plastic effects exerted by endogenous firing potentiation[68].

A variety of studies have found that in healthy individuals, anodal tDCS to dorsolateral PFC (DLPFC) leads to increased cognitive performance[69]. In the treatment of MDD, the anode is located over the left DLPFC, which is hypoactive, helping to improve local activation and regain regular functioning[70]. The cathode is located either over the right DLPFC or the right supraorbital or frontotemporal area, leading to distinct current distributions. In addition, after anodal DLPFC tDCS in patients with schizophrenia, enhanced results on working memory tasks[71], probabilistic learning tasks[72], adaptive control tasks[73], and attention-vigilance tasks[74] have been demonstrated. A consistent feature of these diverse tasks is that they all depend, in part, on cognitive control mechanisms such as goal maintenance mediated by DLPFC.

We suggest a model in which the tDCS, instead of focusing on a single cortical area, could simultaneously target several zones that are part of a common network. Considering the results of our imaging studies, they point to the hypothesis that in schizophrenic patients the DMN is incorrectly activated in conditions that are not typical for such activation (tr-fMRI), while based on the study of connectivity we note

that the DMN is deactivated in rest conditions, which is the normal condition of its activation.

Our views are that tDCS can be useful for restoring the normal connectivity of the different components of the DMN if the electrodes are placed simultaneously in several areas of the parietal cortex, namely the PreCu, PCC and AngG, which can potentially regulate the disrupted connection between the individual components of DMN and thus lead to improved symptoms such as cognitive impairment in schizophrenia.

DBS

DBS is the most invasive focal neuromodulation tool for mental disorders available. This technique allows us to deliver electrical stimulation of GM or white matter in a therapeutic attempt to improve the dysfunctional activity of the brain. DBS is probably the most elegant and complex perfect example of the translational approach – integration of instrumental, neurobiological, neurosurgical, and psychopathological knowledge in performing this precise and innovative psychosurgical procedure. It involves a high-frequency deep-brain stimulation by stereotactic inserted electrodes. It is known to act primarily by functional inhibition around the electrode, but it may also have excitatory effects on local axons and far-reaching excitatory effects[75].

DBS has proven to be beneficial in the treatment of severe mental illnesses like major depression[76], obsessive-compulsive disorder (OCD)[77], Tourette's syndrome[78] and addiction[79]. The use of DBS in patients suffering from schizophrenia is still in its early stages and at present has not been officially approved. There seems to be no consensus regarding the particular brain structures, networks, and circuits which could be clinically beneficial for DBS treatment of schizophrenia. Studies have reported DBS of the habenula[80], nucleus accumbens and ACC[81]. These early experiments indicate the capacity of DBS to have beneficial effects in schizophrenic patients who do not respond to any other treatment. In order to assess the magnitude of the advantages and whether they can be accomplished without psychiatric side-effects, further studies would be needed with thoughtful consideration.

We suggest that the future research on the therapeutic effect of DBS in schizophrenia should focus extensively on two important areas, namely the insula and the PreCu, as they are the key nodes of the SN and DMN — the two brain networks that appear to be disconnected in the paranoid group in our study. We speculate that the enhancement of the altered function of the DMN and SN could ultimately restore the cognitive deficits and the disorganized thought and behavior observed in schizophrenic patients.

CONCLUSION

Psychotic and mood disorders affect a large number of people all over the world and have significant effects for individuals, their loved ones and society. To improve the prognosis and outcome of these disorders, it is crucial to make changes in their management. Unconventional instrumental biomedical methods have proven effectiveness for different psychiatric conditions (*e.g.*, ECT for depression, mania, and catatonia; TMS for drug-resistant depression; tDCS for cognitive enhancement in schizophrenia; DBS for OCD, addiction and severe MDD). However, their usage is still limited, and these tools remain in the shadow of psychopharmacology and psychotherapy.

Results from our studies on cross-validation of tr-fMRI, effective connectivity at rest and the MLM point to some interesting and new therapeutic applications that can modulate the SN and thereby the DMN and FPN function that are impaired in people suffering from schizophrenia. Moreover, these findings could be translated in the protocols of methods like ECT, TMS, tDCS and DBS that have the potential to modulate the network plasticity of the brain. The comprehensive approach towards modifying dysfunctional SN and DMN found in patients with schizophrenia is likely to require a combination of pharmacogenomic testing to inform pharmacotherapy selection and dosing decisions in order to restore the aberrant plasticity of brain networks, together with targeted neurostimulation to trigger network reorganization. However, this approach and the specific mechanisms that influence the complex abnormal interactions between the SN and the DMN are not fully understood and need further investigation.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 May 19; 11(5): 181-200

DOI: 10.5498/wjp.v11.i5.181

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Basic Study

COVID-19 knowledge, risk perception, and information sources among Chinese population

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Author contributions: All authors contributed to the concept of this study; Pan QW, Ma ZR, and Baloch Z designed the study; Baloch Z and Idris S analyzed the data and wrote the manuscript; Pan QW, Ma ZR, and Baloch Z approved the final manuscript; all authors reviewed and approved the final draft.

Institutional review board statement: The protocol used in this study was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee at Northwest Minzu University Lanzhou, China.

Conflict-of-interest statement: The authors declare that they have no competing interests to disclose.

Data sharing statement: The aggregate data supporting findings contained within this manuscript will be shared upon request submitted to the corresponding author.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external

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Abstract

BACKGROUND

Measures for effective control of the coronavirus disease 2019 (COVID-19) pandemic include identifying the causal organisms, applying appropriate therapies, and developing vaccines, as well as improving understanding among the general public.

AIM

To evaluate the knowledge, awareness, perception, and response of the general public to COVID-19 in China.

METHODS

A detailed questionnaire comprising 47 questions designed in both English and Chinese was developed. The survey was conducted *via* WeChat, a multipurpose messaging, social media, and mobile payment app that is widely used by the Chinese population. In total, 1006 participants responded, and most of them were from different provinces of mainland China.

RESULTS

Overall, this comprehensive survey revealed that the general public in China is highly aware of the basic information concerning COVID-19 and its precautions. Interestingly, more respondents (99.3%) were aware of the term severe acute respiratory syndrome (SARS) than COVID-19 (97.2%) and Middle East respiratory syndrome (MERS) (73.4%). Among them, 2.4%, 1.6%, and 0.9% said that they or their family members or friends were affected by COVID-19, SARS, and MERS,

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: November 20, 2020
Peer-review started: November 20, 2020
First decision: December 21, 2020
Revised: January 8, 2021
Accepted: April 9, 2021
Article in press: April 9, 2021
Published online: May 19, 2021

P-Reviewer: Boregowda U
S-Editor: Gao CC
L-Editor: Wang TQ
P-Editor: Li JH

respectively. The majority of the respondents (91.2%) indicated that knowledge about COVID-19 was received mainly from WeChat, followed by TV (89%), friends (76.1%), and QQ (a Chinese instant messaging software service) (57.7%).

CONCLUSION

The general public in China is highly aware of COVID-19 and the necessary precautions. Unexpectedly, 2.8% of the participants were unaware of the current epidemic. The remaining information gaps highlight the necessity of further enhancing awareness and preparedness.

Key Words: COVID-19; Knowledge; WeChat; China; Pandemic; Knowledge

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Core Tip: This study comprehensively evaluated the knowledge, awareness, and perceptions about coronavirus disease 2019 (COVID-19) among the general Chinese population. Overall, the general public is well aware of the COVID-19 epidemic, knows what COVID-19 is, and is familiar with the precautionary measures. Strikingly, this survey indicated that 2.8% of the participants in China were unaware of the current COVID-19 epidemic.

Citation: Ma ZR, Idris S, Pan QW, Baloch Z. COVID-19 knowledge, risk perception, and information sources among Chinese population. *World J Psychiatr* 2021; 11(5): 181-200
URL: https://www.wjgnet.com/2220-3206/full/v11/i5/181.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i5.181

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is now affecting the global population[1]. In addition to significant losses in terms of morbidity and mortality, COVID-19 has imposed major negative impacts on society and the economy in various aspects. COVID-19 was initially sparked in Wuhan, the capital of Hubei Province, and subsequently spread to the entire province and other parts of China, and eventually to the rest of the world[2]. Measures for effective control of outbreaks include identifying the causal organisms, applying appropriate therapies, and developing vaccines, as well as promoting understanding among the general public.

Syndemics is a group of interlinked health issues associated with two or more conditions that interact synergistically and cause an increased disease burden in the population. At this moment, COVID-19 and an array of noncommunicable diseases interact on a social and economic background, which exacerbates its adverse effects[3]. Strict guidelines with specific emphasis on protective measures such as city lockdowns, travel bans, and within-population quarantines were developed by the authorities for controlling the pandemic. As these measures lead to physical inactivity, they also had an adverse impact on health, such as promoting obesity, premature ageing, cardiovascular vulnerability, bone loss, muscle atrophy, decreased aerobic capacity[4], and psychological issues[5-8]. Physical activity is vital for public health[6], as it acts on the cardiovascular and respiratory systems[7].

Furthermore, the effectiveness of epidemic control implementations relies substantially on the support and cooperation of the public. Thus, awareness and knowledge about the epidemic are essential[9-11]. Despite the experience of the SARS outbreak in 2003 in China, the early response to the COVID-19 outbreak was inadequate from both the Chinese authorities and the general public[12]. Subsequent implementation of strict control measures by the authorities with strong support and cooperation from the public finally resulted in the control of COVID-19 in China. However, COVID-19 has grown into a pandemic and may become endemic[13]. Knowledge gaps always exist about disease epidemics, their potential risks, and the clinical spectrum[13]. Thus, we designed and conducted this survey to evaluate the knowledge, awareness, perception, and response of the general public to COVID-19 in China.

MATERIALS AND METHODS

Study design and participants

A detailed questionnaire comprising 47 questions related to COVID-19 with some questions about SARS and Middle East respiratory syndrome (MERS)[14-16] was designed in both English and Chinese. The survey was conducted *via* WeChat, a Chinese multipurpose messaging, social media, and mobile payment app. It is widely used in China, with monthly active users estimated at one billion.

Knowledge about COVID-19, MERS, and SARS was assessed with questions about whether they had heard about these infections, whether they or their family members or friends had been infected, whether they knew what COVID-19 is and knew its causes, whether they knew the zoonotic origin of the infection, whether they ever ate civet or other wild animals, and whether they knew about the death rate from COVID-19. The participants were assessed regarding COVID-19 risks and associated factors along with their knowledge of possible control measures to avoid the infection. The participants were also asked about general signs and symptoms of the disease and from where they obtained information regarding this infection.

Statistical analysis

Descriptive and inferential statistics were calculated using SPSS version 20.0 for Windows (SPSS Inc., Chicago IL, United States). Awareness and knowledge about COVID-19, SARS, MERS, and related factors are shown as percentage values. All independent variables were divided into two or more categories. Variables that were statistically significant in the univariate analyses were included in the final multivariate logistic regression analysis using SPSS. All statistical tests were two-sided, with a P value < 0.05 considered statistically significant.

RESULTS

The questionnaire was completed from March 11 to 14, 2020. In total, 1006 individuals (aged 18-71 years) from all over China participated in the survey by filling out the questionnaires. The majority of our participants (99.3%) were distributed across 29 provinces of China, with 8.7% from Hubei Province and 0.7% residing outside of China (Supplementary Table 1). Among the respondents, 99.1% were Chinese and 0.9% were foreigners residing in China. Based on ethnicity, 65.4% were Hans and 34.6% were from other Chinese ethnic groups or foreigners. Approximately 63% of participants were female. The detailed sociodemographic characteristics of the participants are presented in Table 1.

Interestingly, more respondents (99.3%) were aware of the term SARS than COVID-19 (97.2%) and MERS (73.4%). Among them, 2.4%, 1.6%, and 0.9% said that they or their family members or friends were affected by COVID-19, SARS, and MERS, respectively. Most of the participants (87.4%) believed that COVID-19 is more dangerous than SARS and MERS, while 47.9% of participants answered that the death rate for COVID-19 patients is less than that of SARS and MERS (Table 2). Approximately 81% of respondents answered that SARS-CoV-2 infection could be transmitted through oral, nasal, and eye routes. Up to 69.7% of people believed that the virus has been transferred from animals to humans and that bats (82.4%) are the reservoir for SARS-CoV-2. The proportion of respondents who had recently consumed wildlife meat was found to be 1.4%. A total of 62.4% of individuals thought that a treatment is available for COVID-19 (Table 2).

This study further revealed that the majority of respondents (46.4%) were experiencing psychological pressure along with economic (19.1%) losses due to the current COVID-19 epidemic in China. A total of 69.4% indicated that they still had not resumed their normal life due to the ongoing epidemic. Unfortunately, 1.5% of people replied that they had lost a loved one due to COVID-19. Furthermore, most of the participants (78%) preferred going in private cars for treatment to hospitals in cases of infection, while 2.2% refused to go to hospitals (Table 2).

Knowledge about the signs and symptoms of COVID-19, such as fever, chills, cough, shortness of breath, and flu, was known by 86.3%, 36.9%, 83.4, 79.0%, and 53.3% of the participants, respectively. However, knowledge about other questions related to the disease incubation period was poor (Table 2). Pearson correlation analysis indicated that the risk of acquiring COVID-19 was negatively associated with general information/knowledge and knowledge about precautionary measures (Supplementary Table 2).

Table 1 Demographic characteristics of participants

Variable	Respondents	Percentage (%)
Sex		
Male	373	37.1
Female	633	62.9
Age, yr		
< 30	524	52.1
31-39	170	16.9
40-49	150	14.9
50-59	98	9.7
> 60	64	6.4
Ethnicity		
Han	658	65.4
Others	348	34.6
Residence		
Rural	372	37.0
Urban	634	63.0
Education		
Middle or less	146	14.5
Undergraduate	724	72.0
Master	88	8.7
PhD	48	4.8
Profession		
Farmer	85	8.4
Teacher	134	13.3
Doctor	73	7.3
Nurse	14	1.4
Government	129	12.8
Private	114	11.3
Students	412	41.0
Business	45	4.5
Marital status		
Married	499	49.6
Unmarried	507	50.4
Monthly income (RMB)		
< 3000	498	49.5
3001-5000	265	26.3
5001-10000	179	17.8
> 10000	64	6.4

Multivariate logistic models indicated that urban-background participants turned out to be significantly (P = 0.006) more informed regarding the death rate due to COVID-19 *vs* SARS and MERS (P = 0.006) (Supplementary Table 3). Knowledge about high death rates in patients with comorbidities was significantly associated with sex (P = 0.012), age (P = 0.001), and ethnicity (P = 0.007) (Supplementary Table 2). On the

Table 2 Positive responses on different questions related to epidemiological and clinical knowledge (total *n* = 1006)

	Numbers (*n*)	Percentage (%)
Do you know about COVID-19	978	97.2
Do you know SARS	999	99.3
Do you know MERS	738	73.4
Have you, your family members, or friends got infected with SARS-CoV-2	24	2.4
Did you or your family or friends got infected with SARS-CoV	16	1.6
Did you or your family or friend got infected MERS-CoV	9	0.9
Is COVID-19 more serious/dangerous than SARS and MERS	879	87.4
Do you know deaths due to COVID-19 are less as compared to SARS and MERS	482	47.9
Do you know SARS-CoV-2 transmitted from animals into humans	827	82.2
Have you eaten Civet ever in your life	12	1.2
Have you and your family members consumed meat of wild animals recently	14	1.4
Do you think early detection and treatment will help COVID-19 patient to recover	962	95.6
Comorbidity increases the risk of death due to SARS-CoV-2 infection	862	85.7
Wearing mask and washing hand with soap and water can minimize the risk of SARS-CoV-2 infection	946	94
Is there a cure for COVID-19	628	62.4
If you are feeling unwell, will you disclose it	993	98.7
Is your community center well furnished with basic medical facilities	610	60.6
Are you back to your routine after COVID-19 outbreak	308	30.6
DO you know SARS-CoV-2 can enter to healthy person *via* all (mouth, nose, and eye)	819	81.4
Source/origin of SARS-CoV-2 infection is animal	701	69.7
Bat is source SARS-CoV-2 infection	829	82.4
COVID-19 affected you psychologically	467	46.4
COVID-19 affected you economically	192	19.1
Are you back to your routine after COVID-19 outbreak (no)	698	69.4
Have you lost family member or friend in COVID-19 outbreak	15	1.5
If you are feeling unwell how will you go to hospital (own car)	785	78.0
If you are feeling unwell you will not go hospital	22	2.2
Signs and symptoms		
Fever	868	86.3
Cough	839	83.4
Chills	371	36.9
Breathing difficulty	795	79.0
Flue like symptoms	538	53.5
All above	480	47.7
Do not know	8	0.8

COVID-19: Coronavirus disease 2019; SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

other hand, information about the protective effects of wearing masks and washing hands with soap for at least 30 s was significantly higher among women (P = 0.007) and rural residents (P = 0.007) (Supplementary Table 3). Chinese people, compared to foreigners (P = 0.024), and farmers, compared to other professions (P = 0.001), were

significantly more satisfied with their community health centre facilities (Supplementary Table 4).

The majority of respondents (91.2%) indicated that information about COVID-19 was received mainly from WeChat, followed by TV (89%), friends (76.1%), and QQ (a Chinese instant messaging software service) (57.7%). Some participants said that they received information related to COVID-19 from newspapers (35.5%), magazines (29.2%), WhatsApp (24.9), and Facebook (24.0%), as shown in Figure 1.

DISCUSSION

Preparing the general population for epidemics or pandemics of infectious diseases is not a static or binary exercise but a dynamic state that is continuously changing[16,17]. Therefore, different states prepare their populations with different methods built on their interpretation of disease outbreak threats and global contracts, such as the International Health Regulations[18].

This study represents a comprehensive survey report about the knowledge, awareness, perception, and response of the general public in China regarding COVID-19. Our results indicate that knowledge and awareness of COVID-19 are high among the general Chinese population. Interestingly, the majority of participants said that WeChat was their main source of information, indicating that valuable information about diseases can be effectively communicated among the general public *via* WeChat in mainland China[19]. Moreover, information dissemination through health departments was surprisingly low (48.1%). As 37% of the participants live in rural areas, these people do not regularly engage with doctors, practitioners, or healthcare officials. This might be the possible cause of their low level of knowledge and awareness about different aspects of COVID-19. Interestingly, WhatsApp and Facebook were not the main sources of information for respondents in mainland China; therefore, information and recommendations regarding COVID-19 and other diseases from international stakeholders such as the World Health Organization should use all possible resources to increase knowledge and awareness among the public.

This study was based on an online questionnaire method; hence, limitations such as recall and social desirability biases cannot be excluded. However, the impact of these biases in this study is difficult to assess, as other similar studies have not been conducted so far. The inclusion of innovative interventional methods with informative evaluation plans to monitor the level of knowledge among the community, respond to their needs, and fill the gaps with better preventive methods would be helpful in prospective research.

CONCLUSION

In summary, this study comprehensively evaluated knowledge, awareness, and perceptions about COVID-19 among the general Chinese population. The overall knowledge, awareness, and attitudes about the disease are at a high level, but strikingly, 2.8% of the participants in China were unaware of the current COVID-19 pandemic, which is unexpected. Therefore, we emphasize the importance of initiating health promotion programs to educate the public and healthcare workers about infectious diseases in general for better preparedness for future epidemics and pandemics.

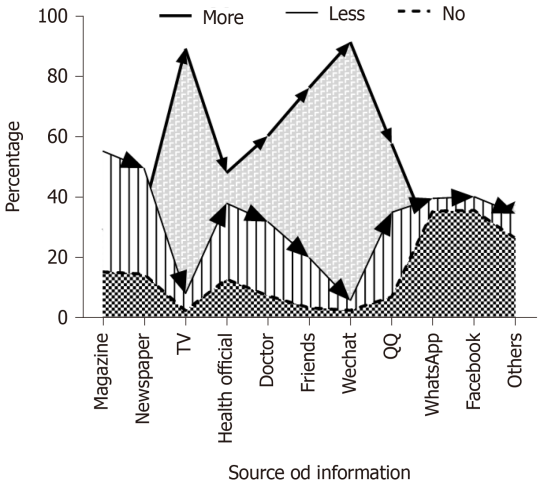


Figure 1 Source of information (little, much, and no) about coronavirus disease 2019. WeChat is a Chinese multi-purpose messaging, social media and mobile payment app. QQ is a Chinese instant messaging software service and web portal. WhatsApp is an American freeware, cross-platform messaging and voice service. Users can send text and voice messages, make voice and video calls, and share images, documents and other media. Facebook is an American online social media and social networking service.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) was initially sparked in Wuhan, the capital of Hubei Province, and subsequently spread to the entire province and other parts of China, and then around the globe. Measures for effective control of outbreaks include identifying the causal organisms, applying appropriate therapies, and developing vaccines, as well as improving understanding among the general public.

Research motivation

COVID-19 has grown into a pandemic and may become endemic. Knowledge gaps always exist about disease epidemics, their potential risks, and the clinical spectrum.

Research objectives

We designed and conducted this survey to evaluate the knowledge, awareness, perception, and response of the general public to COVID-19 in China.

Research methods

A detailed questionnaire comprising 47 questions designed in both English and Chinese was developed. The survey was conducted *via* WeChat, a multipurpose messaging, social media, and mobile payment app that is widely used by the Chinese population. In total, 1006 participants responded from different provinces in mainland China.

Research results

Overall, this comprehensive survey revealed that the general public in China is highly aware of the basic information concerning COVID-19 and the necessary precautions. Interestingly, more respondents were aware of the term severe acute respiratory syndrome than COVID-19 and Middle East respiratory syndrome. The majority of the respondents indicated that knowledge about COVID-19 was received mainly from WeChat, followed by TV, friends, and QQ (a Chinese instant messaging software service).

Research conclusions

We comprehensively evaluated the knowledge, awareness, and perceptions about COVID-19 among the general Chinese population. The overall knowledge, awareness, and attitudes about the disease are at a high level, but strikingly, 2.8% of the participants in China were unaware of the current COVID-19 pandemic, which is unexpected.

Research perspectives

We emphasize the importance of initiating health promotion programs to educate the public and healthcare workers about infectious diseases in general for better preparedness for future epidemics and pandemics.

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World Journal of Psychiatry

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World J Psychiatr 2021 May 19; 11(5): 189-200

DOI: 10.5498/wjp.v11.i5.189

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Uncertainty following an inconclusive result from the BRCA1/2 genetic test: A review about psychological outcomes

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Author contributions: Bramanti SM, Trumello C, Lombardi L, Cavallo A, Stuppia L, Antonucci I and Babore A conceived the study; Bramanti SM and Cavallo A carried out the literature searches and extracted the data; Babore A, Trumello C and Bramanti SM assessed the study quality and wrote the manuscript; Lombardi L, Stuppia L and Antonucci I revised the manuscript.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external

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Abstract

BACKGROUND

An inconclusive result from BRCA1/2 genetic testing indicates that a genetic variant of uncertain significance is detected. This case constitutes the majority of genetic test results, but studies specifically addressing the psychological adjustment of people with inconclusive results are scarce.

AIM

To examine psychological outcomes of receiving an uninformative BRCA1/2 test result.

METHODS

PubMed, PsychInfo, and Cochrane Central Register of Controlled Trials were screened for studies focusing on distress, anxiety, and depression levels in individuals with inconclusive genetic test results. This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method.

RESULTS

Studies on psychological outcomes of inconclusive BRCA1/2 focused on general and specific distress, anxiety, and depression. Overall, they produced mixed results. These inconsistent findings are probably due to the uncertainty caused by this type of result, that may also influence the decisions of individuals about surveillance and prophylactic options, reducing their compliance. In addition, this review highlights specific risk and protective factors that affect psychological adjustment in individuals with an inconclusive genetic testing result.

CONCLUSION

Individuals with inconclusive genetic test results need specific educational programs and support to better understand the meaning of their results in order

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 16, 2021
Peer-review started: February 16, 2021
First decision: March 16, 2021
Revised: March 28, 2021
Accepted: April 21, 2021
Article in press: April 21, 2021
Published online: May 19, 2021

P-Reviewer: Stoyanov D
S-Editor: Fan JR
L-Editor: A
P-Editor: Li JH

to be able to make decisions about surveillance and prophylactic options.

Key Words: Genetic testing; BRCA1/2 mutation; Inconclusive result; Psychological distress; Depression; Anxiety; Review

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Core Tip: Undergoing BRCA1/2 genetic testing can produce a significant psycho-social impact. The possible test results are positive (increased risk of developing cancer), negative (the same probability of developing cancer as the general population), or inconclusive. This last outcome produces a more complex situation, as it means that a deleterious mutation is neither identified nor definitively excluded. Though the inconclusive case constitutes most genetic test results, studies specifically addressing psychological adjustment of people with such a result are scarce. The current review aims to address this gap, highlighting psychological outcomes following this kind of result and highlighting specific risk and protective factors.

Citation: Bramanti SM, Trumello C, Lombardi L, Cavallo A, Stuppia L, Antonucci I, Babore A. Uncertainty following an inconclusive result from the BRCA1/2 genetic test: A review about psychological outcomes. *World J Psychiatr* 2021; 11(5): 189-200
URL: https://www.wjgnet.com/2220-3206/full/v11/i5/189.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i5.189

INTRODUCTION

In the context of breast and ovarian cancer surveillance, genetic screening for the detection of mutations in *BRCA1* (chromosome 13) and *BRCA2* (chromosome 17) genes is a significant advance in cancer care. Each individual carries these two genes, which are responsible for the control and repair of DNA alterations; however, in their mutated form, they are linked to an increased risk of tumor development[1]. These genes are characterized by autosomal dominant inheritance, so one parent has a 50% chance of transmitting them to their children[1,2]. The lifetime risk of developing breast cancer in the general population ranges from 10%-14%, and this risk rises to 85% in women who carry a mutation in the *BRCA1* and *BRCA2* genes[2,3].

For individuals with high cancer history, genetic counselling is proposed. Medical and family histories are collected, and if there is at least 10% likelihood, a buccal smear or a blood sample is taken. The possible test results are positive, negative, or inconclusive[4]. The first one implies that the individual is a carrier of a mutation with an increased risk of developing cancer during his life. A negative result means that the individual is not a carrier of mutation, so he has the same probability of developing cancer as the general population. An inconclusive result produces a more complex situation, as it means that a deleterious mutation is neither identified nor definitively excluded. This may be due to two main reasons: (1) No known BRCA1/2 mutations were found, but a genetic variant of uncertain significance is detected; and (2) Not detecting a mutation in a cancer-affected person who is the first member tested (proband) in a high-risk family[5,6]. In the current review we indistinctly use the terms "inconclusive" and "uninformative" to refer to both the aforementioned situations. Though the inconclusive case constitutes the majority of genetic test results[1,7], research and clinical attention is lacking in this topic, as stated by several authors[5,8].

Undergoing genetic testing and its results can produce a significant psycho-social impact[2,9]. Generally, individual who receives a positive test result reports higher levels of distress, anxiety, and depression[10] while who receives a negative test result reports a decrease in distress levels following the discovery of test results[11]. A recent review of existing literature[12] highlighted that a positive genetic testing results can be traumatic, although not all individuals with such a result experience increased distress. The high distress levels experienced by individuals who receive a positive test results may depend by an increased risk of future diseases and the implications for their whole family[12]. A study highlighted that a possible factor that influences affective states is the perceived risk of developing cancer, regardless of test result[13].

Overall, higher levels of distress, anxiety and depression could depend by some risk factors as having a cancer diagnosis, having a greater history of breast/ovarian cancer, being younger than 40 years old, being unmarried and having high pre-test levels of anxiety and depression[12].

As for those who receive an inconclusive result, the literature is conflictual; some studies identify higher levels of distress in those with an inconclusive result[14] while other studies found that individuals who receive an inconclusive result seem reassured[15]. However, as stated by several authors[12,16], studies specifically addressing psychological adjustment of people with inconclusive genetic test results are scarce. According to Vadaparampil *et al*[8], this gap should be filled, as the topic of inconclusive test results is a key topic deserving clinical and research attention.

Starting from these premises, the main purpose of the current review was to investigate short-, intermediate-, and long-term consequences of receiving uninformative BRCA1/2 test results. To pursue this aim, we analyzed cross-sectional and longitudinal studies which examined anxiety, depression and distress in individuals who receive inconclusive results compared to positive and negative results. In addition, we aimed to highlight risk and protective factors that affect psychological adjustment in individuals with an inconclusive genetic testing result, also considering differences associated with being or not affected by a cancer diagnosis.

MATERIALS AND METHODS

Identification and selection of studies

This systematic review followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analyses[17].

We conducted a comprehensive literature search in PubMed, PsychInfo, and Cochrane Central Register of Controlled Trials. All search results were limited to the last 21 years (1999-2020).

We combined search terms related to genetic counselling and its result [(Genetic*, Familial*, OR Mutation*) and (Inconclusive OR Uncertain) and (Breast* OR BRCA*)] with terms relating to psychological outcomes (Psycho*, Distress, Emot*, Anxiety, OR Depression). The reference sections of previous reviews were also checked to ensure that all relevant studies for this review were included.

Selection of eligible articles

Studies were included if they: Analyzed psychological outcomes of receiving an uncertain result; included adult, human subjects; and were written in the English language.

Exclusion criteria were: Articles not specific to BRCA mutation; articles not reporting psychological outcomes; articles that assessed the impacts of genetic counselling before subjects received genetic test results; and literature reviews, qualitative studies, commentaries, letters to the editor, unpublished articles and doctoral theses, abstracts of conferences, congresses, books, and case-reports.

Following the review by Hamilton *et al*[18], we defined short-term as within 1 mo of genetic testing results, intermediate term between 1 and 6 mo, and long-term over 6 mo.

The eligibility criteria were evaluated according to the following aspects: Participants, intervention, comparison, outcome, and study design. (1) Participants: Human adult participants receiving an uncertain result from genetic testing about the presence of BRCA mutation; (2) Intervention: The focus was not limited on a specific intervention; (3) Comparison: Studies comparing people with inconclusive genetic test results to positive and negative results; (4) Outcomes: We analyzed studies that considered short- (1 mo), intermediate- (1-6 mo), and long- (6+ mo) term psychological outcomes (*i.e.*, general and specific distress, anxiety, and depression); and (5) Study design: We included observational and/or quantitative studies.

Anxiety, depression, and distress (both general and specific) have been the focus of the review as they were the outcome measures most frequently evaluated.

RESULTS

A total of 341 studies were identified; of those, 174 were removed as duplicates. The

titles of the selected studies were double screened by two authors independently, 66 studies were excluded because they were not consistent with the eligibility criteria. The abstract of 101 selected studies and the full text of all potentially relevant articles were double screened and evaluated by two authors independently; discrepancies were resolved by discussion; the following were excluded: 11 were reviews, 46 did not focus on psychological variables, 23 studies involved a sample with a different genetic mutation from BRCA or did not focus on inconclusive results, and 11 had an inadequate study design (qualitative studies, unpublished articles, case-reports, books or abstracts of congresses). A total of 10 articles met our inclusion criteria and were, therefore, considered in this systematic review (Figure 1). Included studies were published between 2002-2017 and were most commonly conducted in the United States, followed by Canada and the United Kingdom. Eight studies were longitudinal (80%) and two were cross-sectional (20%). All the included studies were classified on the basis of the timing of questionnaire administration; most studies (n = 7) assessed also baseline levels of psychological measures before the blood test or buccal smear test.

Only one study considered exclusively short-term psychological outcomes, four studies only intermediate-term, and three studies long-term (Table 1). Sample sizes from the reviewed studies ranged from 48 to 465 (mean = 193.30, standard deviation = 135.14), resulting in a total of 1933 participants. Of these, 38% (n = 730) received inconclusive test results, 32% (n = 620) received negative results, 21% (n = 408) received positive results, 7% (n = 126) decided not to undergo genetic testing, and 2% (n = 49) were still waiting for their test results. Only two studies included male participants; the sample was predominantly female (98%).

Of the reviewed articles, six studies compared people with and without a cancer history. The majority of the sample (73%) had a cancer diagnosis. Only four studies reported the type of cancer diagnosis; of these, 94% had breast cancer, 4% had ovarian cancer, and 2% had both.

Outcome measures of the included studies

The findings were divided into four categories: (1) General distress; (2) Anxiety; (3) Depression; and (4) Genetic testing-specific distress. The tools used for the evaluation of each construct are synthesised in Table 2.

The Brief Symptoms Inventory (BSI)[19-22], the Symptom Checklist 90 Revised (SCL-90)[23-25], the Impact of Event Scale[26,27], the General Health Questionnaire[28,29], and the Hopkins Symptom Checklist[30,31] were used to assess general distress symptoms. Depressive symptoms were assessed using the BSI[6,19,20], the SCL-90[23,24], the Hospital Anxiety and Depression Scale (HADS)[29,32], and the Center for Epidemiologic Studies Depression Scale[25,33].

The BSI[6,19,20], the SCL-90[23,24], the HADS[29,32], and the State Trait Anxiety Invento-ry[25,34] evaluated anxiety symptoms.

Finally, genetic testing-specific distress was evaluated by means of the Multidimensional Impact of Cancer Risk Assessment[6,20,27,35,36].

General distress

The majority of the reviewed studies did not find significant differences in psychological adjustment among individuals who received inconclusive, positive and negative results[22,24,25,29,31]. One study observed higher levels of distress, especially on the somatization scale, in those who received inconclusive results compared with positive and negative results, and people deciding not to undergo genetic testing[21]. Instead, a recent study of Lumish *et al*[27] highlighted that individuals receiving an inconclusive result reported intermediate levels of general distress, higher than negative but lower than positive result.

Schwartz *et al*[31] did not find increased levels of distress in people with inconclusive results compared to positive and negative results, but they did not identify a decrease in distress levels in the intermediate-term (*i.e.*, 1-6 mo) in individuals with inconclusive results, which occurs in those who receive negative results. Two studies found that general distress decreased slightly over time, from pre-test to 6 mo post-test[20,25]. Other studies reported that there were no differences in distress levels from pre-test levels up to 6 mo after genetic test disclosure[22,29].

Regarding differences between cancer affected patients and unaffected patients, overall, unaffected patients with positive or inconclusive results reported higher levels of distress compared to both affected patients and unaffected patients with negative results[27]. Other studies highlighted that having had a cancer diagnosis did not influence distress levels; in fact, they did not detect differences between affected and unaffected patients[21,22,25].

Table 1 Time of psychological outcome measures after genetic test disclosure

Ref.	Average months after genetic test disclosure		
	≤ 1 m	Between 1 and 6 mo	More than 6 mo
Bish *et al*[29], 2002[1]	Y	Y	
Claes *et al*[24], 2004[1]			Y
Graves *et al*[36], 2012[1]			Y
Lumish *et al*[27], 2017			Y
Manne *et al*[22], 2004[1]		Y	
O'Neill *et al*[20], 2006[1]		Y	
O'Neill *et al*[6], 2009		Y	Y
Power *et al*[21], 2011	Y		
Schwartz *et al*[31], 2002[1]		Y	
Smith *et al*[25], 2008[1]	Y	Y	

[1]Studies that assessed also baseline levels of general distress, anxiety, depression and genetic test specific distress (*i.e.*, before genetic test disclosure).
Y: Yes.

In addition to genetic test results, other factors which could increase distress levels in those who receive an inconclusive result may be a cancer diagnosis[27], higher distress levels before genetic testing[25], the intolerance of uncertainty[20], and cancer-related distress[20].

However, there are also some protective factors that could mitigate or decrease distress levels such as marital status[20], partner support, and protective buffering[21].

Anxiety

None of the reviewed studies found differences in anxiety levels among individuals with inconclusive, positive and negative results[24,25,29] except for one study that found that patients with inconclusive results reported higher levels of anxious symptoms after test result disclosure than negative ones[6].

Some studies observed anxious symptoms in the intermediate-term[25] and long-term[6,29]. Two studies of these did not find changes in anxiety levels in the intermediate-term[25,29], while O'Neill *et al*[6] detected a decrease in anxiety over time for individuals who received negative test result and stable levels of anxiety in those who received inconclusive results from the discovery of the test result up to 6 mo later, with a subsequent decrease.

Only one of the reviewed articles that focused on anxiety investigated whether there were differences among affected and unaffected patients and found that there were no differences between them[25].

Overall, some factors that could influence anxiety levels in individuals who receive an inconclusive test results, might be: Higher distress levels before genetic testing[25], higher pre-testing anxiety[6], correctly interpreting the meaning of the genetic test result[24,29], primary appraisal, namely the way people evaluate the importance of a stressful situation[6], and ethnicity[6].

Depression

Four of the included studies focused on depression[6,24,25,29]. The majority of the reviewed studies did not identify differences between those receiving inconclusive, positive and negative results[24,25,29].

Two studies did not identify effects of time on depression in the intermediate-term[25,29]. Only one study analyzed long-term outcomes (6 mo), highlighting that depressive levels were significantly higher in individuals receiving inconclusive results compared to negative[6].

Having received a cancer diagnosis did not influence depressive levels, regardless of the test results[25]. Other factors could influence depressive levels among individuals who receive an inconclusive test result: Misinterpretation of test results[24,29], pre-test depressive levels[6,25], primary appraisal[6], and ethnicity[6].

Table 2 Characteristics of included studies

Ref.	C country	AAim	Study design	Psychological measurements	Sample size and gene mutation status	Personal cancer history
Bish *et al* [29], 2002	United Kingdom	Examine the effects of an uncertain test results affects mood and behavior	Longitudinal	HADS; IES; GHQ-28; Cancer Worry Scale	Total sample = 48. Positive = 0. Negative = 0. Inconclusive = 48	History = 48. No history = 0
Claes *et al*[24], 2004	United States	Evaluate the impact of a genetic test result	Retrospective	IES; STAI; SCL-90; UCL; Semi structured-interview	Total sample = 48. Positive = 18. Negative = 6. Inconclusive = 24	History = 48. No history = 0
Graves *et al*[36], 2012	United States	Evaluate the long-term psychosocial impact of the genetic test result	Longitudinal	IES; STAI; BSI; PSS; MICRA	Total sample = 465. Positive = 144. Negative = 60. Inconclusive = 261	History = 390. No history = 75
Lumish *et al*[27], 2017	United States	Investigate the psychological outcomes of people who undergoing genetic test	Cross-sectional	IES; MICRA; SWD; AT-20	Total sample = 232. Positive = 25. Negative = 173. Inconclusive = 34	History = 129. No history = 103
Manne *et al*[22], 2004	United States	Evaluate the distress related to undergoing the genetic test	Longitudinal	IES; BSI; Discussion about testing; Sharing of concerns; Comfort sharing concerns; Protective Buffering; Relationship strain; Support/encouragement for testing; Perceived negative partner behaviors.	Total sample = 144. Positive = 38. Negative = 15. Inconclusive = 91	History = 115. No history = 29
O'Neill *et al*[20], 2006	United States	Explore psychological consequence and the tolerance of uncertain in women who receive an inconclusive test result	Longitudinal	IES; BSI; MICRA; IUS	Total sample = 64. Positive = 0. Negative = 0. Inconclusive = 64	History = 64. No history = 0
O'Neill *et al*[6], 2009	United States	Assess differences in distress levels over time	Longitudinal	IES; BSI; MICRA	Total sample = 209. Positive = 0. Negative = 190. Inconclusive = 19	History = 209. No history = 0
Power *et al*[21], 2011	Canada	Examine levels of distress in people undergoing genetic test	Cross-sectional	History Questionnaire; Feelings about Test Results Measure; Psychosocial Needs Questions; BSI-18	Total sample = 318. Positive = 85. Negative = 51. Inconclusive = 33. Attending result = 49. Not undergo genetic test = 100	History =160. No history = 158
Schwartz *et al*[31], 2002	United States	Examine the long-term psychological impact of receiving BRCA 1/2 test result	Longitudinal	IES; HSCL-25	Total sample = 279. Positive = 78. Negative = 58. Inconclusive = 143	History = 186. No history = 93
Smith *et al*[25], 2008	United States	Evaluate psychological consequences of genetic test results	Longitudinal	GSI; IES; PSS; STAI; CES-D; QoLS	Total sample = 126. Positive = 20. Negative = 67. Inconclusive = 13. Not undergo genetic test = 26	History = 58. No history = 68

HADS: Hospital Anxiety and Depression Scale; QoLS: Quality of Life Scale; CES-D: Center for Epidemiologic Studies Depression Scale; STAI: State-Trait Anxiety Inventory; IES: Impact of Event Scale; MICRA: Multidimensional Impact of Cancer Risk Assessment; UCL: Utrecht Coping List; SCL-90: Symptom Checklist-90; BSI: Brief Symptom Inventory; BSI-18: Brief Symptom Inventory-18; GSI: Global Severity Index; PSS: Perceived Stress Scale; SWD: Satisfaction with Decision Instrument; AT-20: Revised Scale for Ambiguity Tolerance; IUS: Intolerance of Uncertain; HSCL-25: Hopkins Symptom Checklist-25; GHQ-28: General Health Questionnaire-28.

Genetic testing-specific distress

Four of the included studies focused on genetic testing-specific distress[6,20,27,36], which was assessed only after genetic test disclosure. All the reviewed studies measured specific distress in the long-term[6,27,36] except for one study that assessed it in the intermediate-term[20].

Two studies found that inconclusive results were associated with lower levels of genetic testing-specific distress than positive test results[27,36] but higher than negative results[27,36].

Higher levels of genetic testing-specific distress were observed from 1-6 mo and 1 year after genetic test disclosure[6,20,36]; specifically, individuals with inconclusive

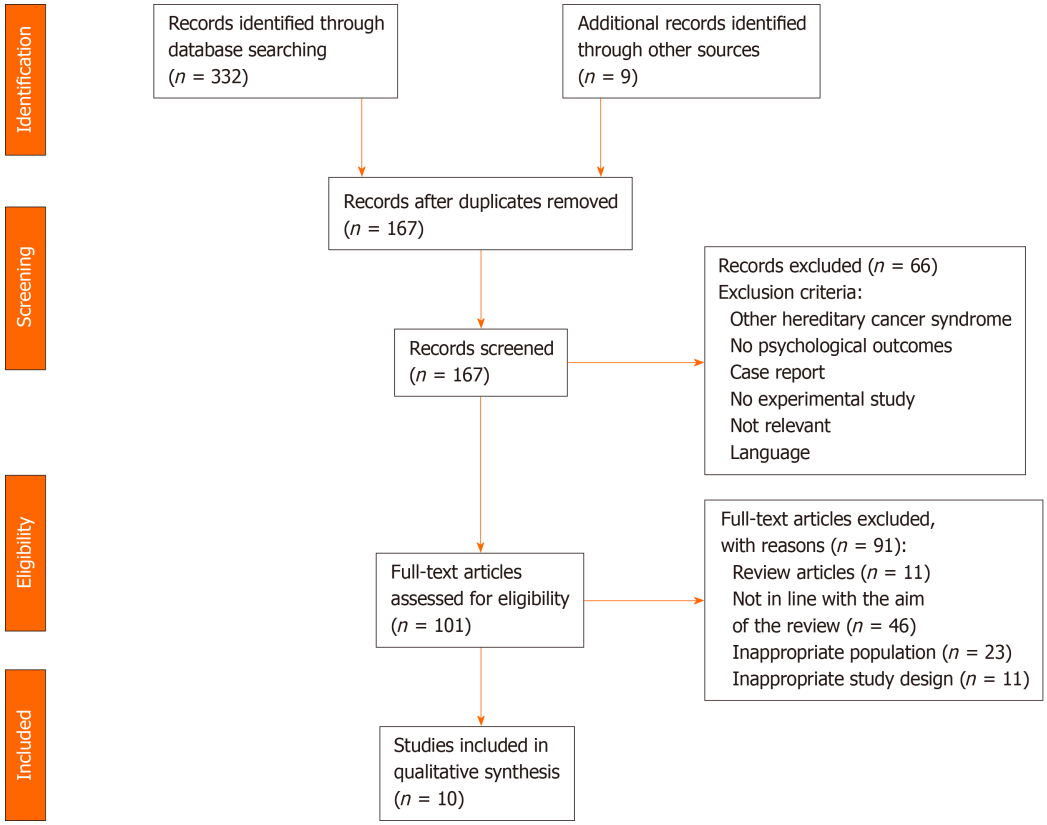


Figure 1 Flow chart of selection and inclusion process, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

results reported higher levels of specific distress persisting even 1 year after test disclosure[6]. O'Neill *et al*[6] detected that distress levels among inconclusive results stayed stable over time and decreased among negative results.

Individuals affected by cancer who receive inconclusive results showed higher levels of distress related to genetic testing than unaffected individuals with inconclusive results, affected carriers, and both affected and unaffected non-carriers[27]. On the contrary, Graves *et al*[36] identified that mutation carriers with a cancer diagnosis had higher levels of distress than affected individuals with uncertain results.

In general, some potential risk factors that could influence genetic testing-specific distress in individuals who receive an inconclusive result are higher pre-test perceived risk[6,20], lower education level[27,36], younger age[27,36], ethnicity[6,36], lower genetic knowledge[27], coping with uncertainty[20], confusion regarding the interpretation of test results[27], pre-test distress[6,36], pre-test anxiety[36], and stronger levels of primary appraisal[6]. Some protective factors, such as being married[36] and stronger secondary appraisal[6], can reduce distress related to genetic testing.

DISCUSSION

The main purpose of the current review was to investigate the consequences of receiving inconclusive results from BRCA1/2 genetic testing on psychological outcomes such as general distress, anxiety, depression, and genetic testing-specific distress. To our knowledge, our review is the first to explore the short-, intermediate-, and long-term psychological effects of receiving inconclusive results in both affected and unaffected patients, as previous reviews were mainly based on individuals who receive a positive or a negative result[12,13,37]. From the analysis of the selected articles, overall different results were found.

Most studies (five of the ten considered) did not report differences in levels of general distress, anxiety, and depression among individuals with inconclusive results, as compared with both positive and negative results[22,24,25,29,31]. Other studies

have found that those who receive inconclusive results experience higher levels of general and specific distress, anxiety, and depression than who have a negative result[6,27,36], but lower than positive ones[27,36]; and finally, a study identified that the inconclusive results caused greater levels of general distress when compared with both positive and negative results[21].

The differences detected from the reviewed studies might depend on the different tools used to assess distress, anxiety, and depression, which might not be sufficiently sensitive in this field[12]. As evidenced by a study by Power *et al*[21], individuals with an uninformative BRCA1/2 test result reported higher levels of distress, specifically in the somatization scale, so it could be that this subgroup of patients experienced distress through the body. Hence, it could be useful to develop more sensible tools, specifically addressing this field.

Although no differences were found between negative and inconclusive results, there was no decrease over time in the levels of distress, anxiety, or depression, which instead occurred in individuals with a negative result[6,31]. A possible explanation for these results might be the lack of relief from this type of test result[16] and having to copy with the uncertainty[21,24,29,38,39]. Indeed, individuals who have difficulty in coping with uncertainty have higher levels of ongoing distress[20]. The uncertainty related to this type of result also influences the decisions of individuals about surveillance and prophylactic options; only a fraction of patients who receive this type of result decides to increase cancer screening[27]. Moreover, some patients determine not to carry out preventive surgery, as they need a more certain result before deciding on this irreversible option[24], from which psychological benefits might be derived due to the cancer risk decrease[40], or it can also lead to adverse psychological impacts and dissatisfaction[41-43]. Graves *et al*[36] identified that having prophylactic surgery does not reduce distress levels but only the perceived risk of developing cancer.

Two studies showed that individuals with a cancer diagnosis have greater levels of distress, anxiety, and depression than those without a previous cancer diagnosis[27,36]; in the group of affected people, being mutation carriers[36] or having received an inconclusive result[27] were associated with a worse psychological adjustment. Patients with a recent cancer diagnosis could represent a population more vulnerable to higher levels of distress, anxiety, and depression due to the impact of the diagnosis and its treatment[44,45]. Other studies did not find differences between affected and unaffected patients[20,25,31]. A possible explanation for these inconsistent results could be the psychological benefit that affected patients derived from genetic testing[12,37], because medical surveillance protocols make the process predictable and understandable[37]. Due to this, affected patients and individuals who receive a positive test result might be better able to cope with this situation than individuals who have to cope with the uncertainty[20,46,47].

Apart from having had a cancer diagnosis[27,36], other factors that influence the psychological outcomes related to genetic test disclosure also emerged from the current review. Among the major risk factors are: Higher pre-test levels of distress and anxiety[6,24,25,31], younger age[6,22,27,36], correctly interpreting the meaning of the test result[24,29], intolerance of uncertainty[20], use of the primary appraisal[6], higher perceived risk before genetic testing[6,20], having a family history of cancer[25,36], lower education level[27,36], lower genetic knowledge[27], having children[36], lower income[36], and belonging to a minority ethnicity[6]. Regarding appraisal, it consists in the evaluation of the relevance of a stressful event such as genetic testing and/or cancer diagnosis[48,49]. Some studies have shown that different coping and evaluation strategies influence distress and stress levels; using a higher primary appraisal and emotional suppression are associated with higher levels[50,51], while increased use of secondary appraisal and cognitive reappraisal are associated with better psychological outcomes[50,52].

In addition to secondary appraisal and cognitive reappraisal, other factors could decrease distress levels such as being married[20,36], having partner support[22], having a bilateral salpingo-oophorectomy[36], and protective buffering[22].

This review revealed that those who receive inconclusive results are a subgroup of patients who need educational programs and more pre-test information to better understand the meaning of their test so they can make decisions about surveillance and prophylactic options.

This literature review has some limitations. First, only a few studies were included in this review because the majority of studies focus on the psychological outcomes of those who receive positive or negative results, although inconclusive results are the most common[1,7]. Another limitation is that the studies we analyzed included different standardized measures concerning distress, anxiety, and depression. It could be that these standardized tools are not sufficiently sensitive in this field and that those

who receive positive, negative, and inconclusive results experience emotional distress differently. Moreover, the sample is unbalanced, as some studies exclusively include patients affected by a cancer diagnosis, a factor that contributes to experiencing higher levels of distress, anxiety, and depression. Finally, there was high variability between the time elapsed from the genetic test to the administration of the psychological questionnaires among the reviewed articles, and not all the reviewed studies administered the questionnaires at the same time to all patients. These limitations lead us not to generalize our results.

CONCLUSION

The results of this systematic review give a fuller picture of the psychological impact of receiving inconclusive results and can help genetic counsellors, health professionals, and researchers to provide more support to this subgroup of patients, by providing adequate information about the meaning of inconclusive genetic test result and its implications in terms of risk to develop cancer. The present review could also be able to improve the knowledge of experiences related to coping with uncertainty, suggesting which are the psychological aspects to consider when working with this type of patients. There is still much to understand in this difficult context, and it is necessary to take into greater consideration those who receive inconclusive results in the research and pre-test and post-test educational program to fully explain to people that inconclusive results do not exclude the possibility that they still might face a higher risk of developing ovarian or breast cancer. These considerations are required in health care contexts to provide adequate psychosocial support for people undergoing genetic testing.

ARTICLE HIGHLIGHTS

Research background

The majority of BRCA1/2 genetic test consists of an inconclusive result, which produces a complex situation, as it means that a deleterious mutation is neither identified nor definitively excluded.

Research motivation

Studies specifically focusing on the psychological adjustment of people with inconclusive results are scarce and a systematic review on this topic is missing.

Research objectives

The principal purpose of this review was to examine short-, intermediate-, and long-term psychological outcomes of receiving an uninformative BRCA1/2 test result, with regard to distress (both general and genetic testing-specific), anxiety, and depressive levels. A further purpose was to highlight risk and protective factors affecting psychological adjustment in individuals with an inconclusive genetic testing result, also considering differences associated with being or not affected by a cancer diagnosis.

Research methods

The guidelines of Preferred Reporting Items for Systematic Review and Meta-Analyses were followed in the current review. A comprehensive literature search in PubMed, PsychInfo, and Cochrane Central Register of Controlled Trials was carried out. Search results referred to the last 21 years (1999-2020).

Research results

Studies on psychological outcomes of inconclusive BRCA1/2 focused on general and specific distress, anxiety, and depression. Overall, they produced mixed results. These inconsistent findings are probably due to the uncertainty caused by this type of result, that may also influence the decisions of individuals about surveillance and prophylactic options, reducing their compliance. In addition, this review highlights specific risk and protective factors that affect psychological adjustment in individuals with an inconclusive genetic testing result.

Research conclusions

This review highlights that individuals who receive an inconclusive result are a subgroup of patients who need educational programs and more pre-test information to better understand the meaning of their test in order to make adequate decisions about surveillance and prophylactic options.

Research perspectives

Overall, the current review highlights the importance to address two main issues in this field: From a research perspective, it is recommended the development of tools more sensible to detect the psychological outcomes of inconclusive BRCA1/2 genetic test results; from a clinical perspective, health professionals and genetic counsellors should provide more psychoeducational support to this subgroup of patients about the meaning and the management of the uncertainty associated with their condition.

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Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 June 19; 11(6): 201-264



Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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World Journal of Psychiatry

Monthly Volume 11 Number 6 June 19, 2021

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WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, *etc*.

INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJP* as 3.545; IF without journal self cites: 3.545; Ranking: 46 among 155 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Yun-Xiaojian Wu*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
June 19, 2021

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https://www.wjgnet.com/bpg/gerinfo/204

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ONLINE SUBMISSION
https://www.f6publishing.com

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E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 June 19; 11(6): 201-214

DOI: 10.5498/wjp.v11.i6.201

ISSN 2220-3206 (online)

REVIEW

How do serotonergic psychedelics treat depression: The potential role of neuroplasticity

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Author contributions: All authors participated sufficiently in the work to take public responsibility for its content; all authors provided substantial contributions to conception and design of the manuscript, contributed to drafting the article and revising it critically for important intellectual content and provided final approval of the version that was submitted.

Supported by Department of Veteran's Affairs, Veteran's Health Administration (Career Development Award), No. 7IK2BX003308 (to Ramanathan D); Start-up Funds from the UCSD Department of Psychiatry (to Ramanathan D); and The Burroughs Welcome Fund (Career Award for Medical Scientists), No. 1015644 (to Ramanathan D).

Conflict-of-interest statement: Dr. Zisook S receives grant support from COMPASS Pathways.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution

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Abstract

Depression is a common mental disorder and one of the leading causes of disability around the world. Monoaminergic antidepressants often take weeks to months to work and are not effective for all patients. This has led to a search for a better understanding of the pathogenesis of depression as well as to the development of novel antidepressants. One such novel antidepressant is ketamine, which has demonstrated both clinically promising results and contributed to new explanatory models of depression, including the potential role of neuroplasticity in depression. Early clinical trials are now showing promising results of serotonergic psychedelics for depression; however, their mechanism of action remains poorly understood. This paper seeks to review the effect of depression, classic antidepressants, ketamine, and serotonergic psychedelics on markers of neuroplasticity at a cellular, molecular, electrophysiological, functional, structural, and psychological level to explore the potential role that neuroplasticity plays in the treatment response of serotonergic psychedelics.

Key Words: Serotonergic psychedelics; Psychedelics; Depression; Antidepressants; Neuroplasticity; Ketamine; Hallucinogens

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Core Tip: Depression is a common mental disorder and one of the leading causes of disability around the world. Monoaminergic antidepressants often take weeks to months to work and are not effective for all patients. This review specifically compares the effects of serotonergic psychedelics with other antidepressants on plasticity at

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 15, 2021
Peer-review started: February 15, 2021
First decision: March 30, 2021
Revised: April 7, 2021
Accepted: May 20, 2021
Article in press: May 20, 2021
Published online: June 19, 2021

P-Reviewer: Brog NA, Zhang D
S-Editor: Gao CC
L-Editor: A
P-Editor: Li JH

multiple levels of nervous system functioning.

Citation: Artin H, Zisook S, Ramanathan D. How do serotonergic psychedelics treat depression: The potential role of neuroplasticity. *World J Psychiatr* 2021; 11(6): 201-214
URL: https://www.wjgnet.com/2220-3206/full/v11/i6/201.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i6.201

INTRODUCTION

Depression is a common mental disorder, and considered to be a major contributor to the overall global burden of disease, affecting an estimated 300 million people worldwide[1]. We have known for more than 60 years that medications with antidepressant action increase monoaminergic transmission[2]. Since imipramine was first introduced in 1957, numerous antidepressants have been developed with increasing specificity for the monoamine systems, including agents selective for serotonin, dopamine and norepinephrine. Surprisingly, while these agents lead to an immediate change in monoaminergic neurotransmission, they typically require at least 4 wk of treatment before leading to beneficial effects, and they are only effective around 30%-40% of the time. These observations have led to the conclusion that, rather than treating a "serotonin deficit" (or some other monoamine deficit) antidepressants may work by promoting some form of neuroplasticity in brain circuits that are relevant to depression[3].

Neuroplasticity is a general term that encompasses molecular, cellular, electrophysiological, structural, functional and psychological changes in the brain. Neuroplasticity underlies our ability to learn and is important for recovery after injury [4]. However, the neuroplasticity model of depression suggests that maladaptive plasticity can also lead to problems, such as those that occur in major depressive disorder (MDD). Antidepressants may work in part by harnessing the power of neuroplasticity to change brain circuits driving maladaptive cognitions and behaviors and thereby improve symptoms[5]. This neuroplasticity-based theory of depression and antidepressant action may also provide an explanatory model for how the novel antidepressant, ketamine, exerts its antidepressant effects.

Ketamine modulates glutamate receptors: It is a non-competitive antagonist at the glutamate N-methyl-D-aspartate (NMDA) receptors (and its metabolite, hydroxynorketamine acts on AMPA receptors). It has been utilized for decades as a dissociative anesthetic. In the early 2000s, the intravenous formulation was discovered to have rapid antidepressant effects at sub-anesthetic doses[6]. Since then, numerous randomized controlled trials have replicated ketamine's antidepressant effects[7-9]. In the last few years the S+ enantiomer of ketamine, esketamine, has received an FDA indication for treatment resistant depression and acute MDD with suicidal ideation or behavior. Due to its non-traditional mechanism of action as well as its rapid effects, ketamine has broadened our understanding of the possible mechanisms behind depression and antidepressant action; and has contributed to the shift in focus from monoamine functioning to neuroplasticity as a target for antidepressant action.

Since the emergence of glutamatergic agents as new approaches to the treatment of MDD, we have also witnessed renewed enthusiasm for the potential therapeutic role of serotonergic psychedelics. Serotonergic psychedelics encompass a broad category of compounds including lysergic acid diethylamide (LSD), psilocybin, mescaline, dimethyltryptamine (DMT, an active ingredient of ayahuasca), and other derivates that induce non-ordinary states of consciousness, and act as agonists or partial-agonists at the serotonin 2A (5-HT_{2A}) receptor[10-12]. Serotonergic psychedelics have been used for thousands of years in traditional medicine and religious ceremonial settings[11]. In the 1940s, LSD played an increasingly important role in the field of psychiatry in clinical and research settings until the end of the 1960s when psychedelics were made illegal and clinical research abruptly ceased[13]. More recently, clinical research with serotonergic psychedelics has slowly started to reappear. Recent clinical research in the context of psychedelic-assisted psychotherapy, has demonstrated the efficacy of psilocybin in treatment resistant depression[14], in MDD [15], and in cancer-related anxiety and depression, with positive effects lasting up to several months after treatment[16]. Similarly recent trials with ayahuasca in recurrent

MDD and in treatment resistant MDD suggest its potential efficacy for MDD[17]. Although clinical trials with LSD are limited, a randomized control double-blind crossover study of LSD in healthy subjects demonstrated lasting changes in positive attitudes about life, positive mood changes, positive social effect and positive changes in well-being[18]. It is important to note that psychedelics may also be associated with transient anxiety, negative affect, and psychosis, which appears to be more common in unprepared users or users with vulnerability to psychosis, however there is no evidence of prolonged psychotic reactions in modern clinical trials when individuals are properly screened[19]. While these early findings suggest that psychedelics may have a potential therapeutic benefit in certain patient populations, the antidepressant mechanism of serotonergic psychedelics remains poorly understood.

One hypothesis is that all antidepressants share, in common, efficacy in driving neuroplasticity relevant to depression circuits. This paper seeks to briefly review the changes in neuroplasticity associated with MDD, and the larger established literature demonstrating the role that neuroplasticity plays in the therapeutic effect of classic antidepressants and ketamine. We will use this as a basis for exploring what is known about serotonergic psychedelics on markers of neuroplasticity (Figure 1).

MOLECULAR CORRELATES OF PLASTICITY ASSOCIATED WITH MDD, CLASSIC ANTIDEPRESSANTS AND PSYCHEDELIC AGENTS

Neurotrophic factors play an important role in neuroplasticity. Neurotrophic factors are a family of molecules that, by binding to specific neurotrophic receptors, support growth, survival, differentiation and synaptic plasticity of neurons. Brain derived neurotrophic factor (BDNF) is a key neurotrophic factor involved in most forms of synaptic plasticity. By binding to its corresponding receptor tropomyosin receptor kinase B (TrkB), BDNF activates intracellular pathways that play an important role in the survival and differentiation of neurons and during synaptogenesis[20-22].

Alterations in BDNF-TrkB signaling have been associated with depression in both humans and animals models[23]. In multiple rodent models of chronic, intermittent, or social defeat stress, BDNF-TrkB signaling has been found to be decreased in the prefrontal cortex (PFC) and hippocampus[24,25]. Chronic stress also may increase BDNF/synaptic plasticity in the amygdala and nucleus accumbens[25], suggestive of maladaptive plasticity. In humans, decreased blood levels of BDNF, and cortical expression of BDNF (measured in postmortem studies) have been noted in subjects with MDD[26,27]. Lower levels of BDNF and TrkB expression have also been found in the hippocampus and PFC of subjects who had died by suicide[28].

Typical antidepressants seem to work in part by activating BDNF/TrkB pathways. Chronic antidepressant treatment has been shown to increase BDNF and TrkB receptor mRNA expression in the hippocampus[29] and heterozygous BDNF knockout mice show an impaired antidepressant response[24]. The antidepressant effect of ketamine has also been associated with an increase in BDNF levels in several studies[30,31] and as with typical antidepressants, heterozygous BDNF knockout mice do not show the typical anti-depressant effects of ketamine[32]. Moreover, NMDA antagonists (*e.g.*, memantine) that do not increase BDNF also do not show antidepressant effects, providing further evidence that it is the mechanism of plasticity, rather than NMDA antagonism, that mediates the antidepressant effects of ketamine[33]. This is further bolstered by recent evidence that direct activation of AMPA receptors by a metabolite of ketamine, hydroxy-nor-ketamine, may be sufficient to increase BDNF and induce an antidepressant response[30]. Down-stream from BDNF, there is much evidence that antidepressants like ketamine work *via* TrkB-induced activation of mTOR[34,35]. In animal models, this mTOR pathway seems critical for the rapid effects of ketamine[36].

In vitro research suggests serotonergic psychedelics can also rapidly increase BDNF levels[37]. Cortical neurons were treated with DOI (a psychedelic amphetamine), DMT or LSD for 24 h before measuring *BDNF* gene and protein expression using droplet digital polymerase chain reaction and enzyme-linked immunosorbent assay, respectively. Although serotonergic psychedelics did not increase the presence of the BDNF transcript they did result in a 2-fold increase in BDNF protein levels[37]. In human trials, a study in Brazil demonstrated that a single dose of ayahuasca in healthy controls (HCs) and patients with treatment resistant depression led to higher levels of serum BDNF which has been previously negatively correlated with depressive symptoms[38]. Similarly, a recent study of low doses of LSD demonstrated increased serum BDNF levels in HCs at 4 h and 6 h after administration, compared to placebo [39].

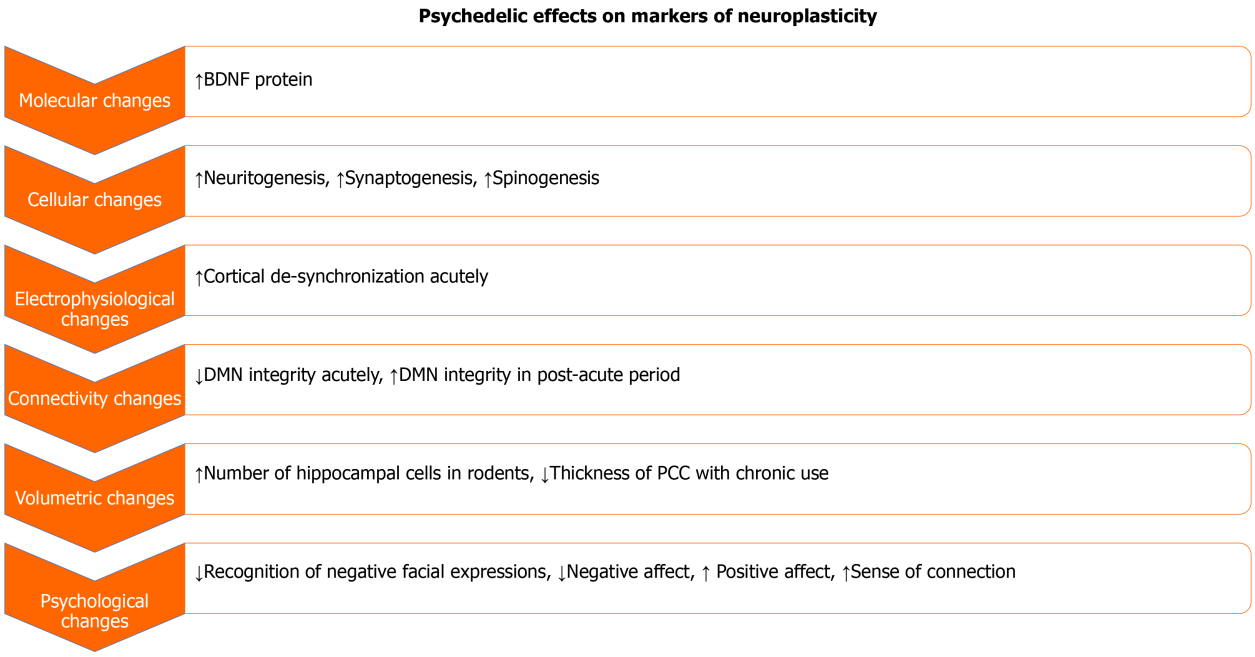


Figure 1 Psychedelic effects on markers of neuroplasticity. At the molecular level serotonergic psychedelics have been associated with increases in brain derived neurotrophic factor protein; at the cellular level serotonergic psychedelics have been associated with increases in neuritogenesis, spinogenesis, and synaptogenesis; at the electrophysiological level serotonergic psychedelics have been shown to lead to cortical desynchronization acutely, less is known about the long term electrophysiological changes although; at the level of functional connectivity serotonergic psychedelics lead to a decrease in default mode network (DMN) integrity acutely but longer-term they may lead to a normalization of DMN integrity; less data exists about volumetric changes with serotonergic psychedelics although in rodents hippocampal neurogenesis has been observed and in long term ayahuasca users decreased thickness of the posterior cingulate cortex has been observed; at a psychological level serotonergic psychedelics have been associated with changes in emotional processing specifically: decreased negative affect, increased positive affect, and an increased sense of connection to the self, others, and the world. BDNF: Brain derived neurotrophic factor; DMN: Default mode network; PCC: Posterior cingulate cortex.

CELLULAR CORRELATES OF PLASTICITY ASSOCIATED WITH CHRONIC STRESS, CLASSIC ANTIDEPRESSANTS AND PSYCHEDELIC AGENTS

There is a large body of literature demonstrating that chronic stress, of various forms, leads to atrophy of prefrontal and hippocampal dendrites[40-43] and synapse loss in those brain regions[44-46]. By contrast, chronic stress models show increased spine density in the basolateral amygdala and nucleus accumbens[47,48]. Postmortem studies in humans are limited but have demonstrated similar findings. For example, there is reduced dendritic branching in the hippocampus and PFC[49] with reduced synapse number in the PFC of depressed subjects[50]. In rodent models of depression, there is evidence that chronic antidepressant treatment can block or reverse some of the above noted changes, including dendritic atrophy and spine loss in the hippocampus and the PFC[51]. Ketamine has also been observed to rapidly increase the number of spine synapses in layer V neurons of the mPFC of rodents in association with its antidepressant behavioral response, and with a similar time course in which the antidepressant effects occur[36,52,53].

Recent research on serotonergic psychedelics suggests that they, likewise, promote rapid dendritic and axonal remodeling. A detailed *in vitro* report observed increased dendritic arbor complexity when cortical neurons were treated with the serotonergic psychedelics (DMT, DOI, LSD, and psilocin) as well as the entactogen (MDMA) which appeared to arise from an increase in number of dendritic branches and the total length of branches[37]. The effects were even greater to those seen when cortical neurons were treated with ketamine at similar doses. These effects were not observed after treatment with serotonin or D-amphetamine. The *in vivo* effects of serotonergic psychedelics on neuritogenesis were measured in this study and drosophila larvae treated with LSD and DOI were observed to have increased dendritic branching of class 1 sensory neurons. Serotonergic psychedelics also had an effect on spinogenesis in rat cortical cultures treated with DOI, DMT, and LSD showed an increase of dendritic spines, with LSD doubling the number of spines observed. Adult rats treated with an intraperitoneal dose of DMT also showed a significant increase in synaptic spine density in the PFC 24 h after dosing, coupled with an increase in excitatory post

synaptic currents (EPSCs). Interestingly, the effect on neuritogenesis and spinogenesis in cortical neurons was blocked by a TrkB antagonist, ANA-12 and by treatment with rapamycin, an mTOR inhibitor. Thus, this study demonstrated rapid effects of serotonergic psychedelics on neuritogenesis and synaptogenesis are likely mediated by TrkB and mTOR pathways. The effects of serotonergic psychedelics on neuritogenesis and spinogenesis in cultured rat cortical neurons was also reduced by inhibition of the 5-HT_{2A} receptor with ketanserin, a 5-HT_{2A} receptor antagonist, suggesting that activation of 5-HT_{2A} receptor by serotonergic psychedelics may play a role in their neuritogenesis and synpatogenic properties[37].

ELECTROPHYSIOLOGICAL MECHANISMS UNDERLYING RAPID PLASTICITY ASSOCIATED WITH KETAMINE AND SEROTONERGIC PSYCHEDELIC AGENTS

We have described above how ketamine and serotonergic psychedelics have been shown to promote rapid synaptic plasticity, with this plasticity possibly mediated *via* BDNF/TrkB and mTOR pathways. However, one question is why ketamine and serotonergic psychedelics have such rapid effects on plasticity. One hypothesis is that they do so because they induce molecular/cellular correlates of plasticity while simultaneously activating brain circuits in ways that amplifies or drives activity-dependent plasticity[22].

To understand how serotonergic psychedelics might result in rapid plasticity, we reviewed the evidence around whether such agents modify brain activity in a way that, like ketamine, might drive activity-dependent plasticity. Ketamine has long been shown to increase cortical excitability[54]. These changes may occur by suppressing activity of inhibitory neurons preferentially[55-57], resulting in an overall state of disinhibition. More recent work has shown that that ketamine-induced antidepressant effects are specifically linked with inhibition of somatostatin neurons[58] resulting in increases in excitability of parvalbumin in addition to glutamatergic neurons and thus protection of spines that would otherwise have been pruned[59]. Evidence from humans corroborates that there is a net increase in both glutamate and GABA (gamma-aminobutyric acid) concentrations in PFC measured using proton spectroscopy after ketamine suggesting that, in humans too, there is a relative disinhibition of prefrontal cortical activity[60]. This data is verified using *in vivo* electrophysiology as well. Multiple studies, across both humans and animals, suggest that ketamine (and its metabolite, hydroxy-norketamine) results in a clear increase in gamma activity (30-80 Hz activity, a useful index of an increase in cortical excitability [61,62].

Some research suggests that serotonergic psychedelic drugs may directly modulate prefrontal cortical activity, leading to activity-dependent plasticity, *via* 5-HT_{2A} receptor activation in the cortex, though it appears to do so in a way very different then ketamine[63]. The 5-HT_{2A} receptor is expressed in deep layer V pyramidal neurons and GABAergic (particularly parvalbumin, PV+) neurons[63,64]. Activation of the 5-HT_{2A} receptor depolarizes and directly excites a subpopulation of deep Layer V pyramidal neurons[65,66], leading to an increase in glutamatergic EPSCs[67-70]. There are reports that pyramidal neurons show both increases and decreases in spiking in response to 5-HT_{2A} agonists, though typically a higher proportion of pyramidal neurons are increased[71-73]. However, unlike ketamine, serotonergic psychedelics like DOI and 5-MeO-DMT actually reduce low-frequency oscillations[71,72] and gamma oscillations [73]. Data from humans also shows that serotonergic psychedelics are all associated with a broadband reduction of power less than 100 Hz[74-77].

In summary, while there is some preliminary evidence that both ketamine and serotonergic psychedelics increase molecular and cellular aspects of synaptic plasticity (activation of BDNF/TrkB pathways; increased synapse/dendritic structure), the mechanisms by which ketamine and serotonergic do this seem to be quite different. With ketamine, there is evidence of an increase in gamma activity/excitability in the cortex, which could serve to activate activity-dependent mechanisms of plasticity and may explain some of the rapid effects observed. With serotonergic psychedelic agents, changes in activity have been shown for certain deep pyramidal cells, but overall evidence from *in vivo* studies suggests that there is not a global level of disinhibition or increase in neural synchrony as a general or wide-spread phenomenon during psychedelics exposure.

PLASTICITY WITHIN DEFAULT-MODE-NETWORK STRUCTURES

Neuroplasticity may also be observed on the level of changes in brain networks[78]. The literature suggests that symptoms of depression are associated with network alterations in "default-mode" brain networks, as well as in salience, affective and cognitive control/executive function brain networks[79]. The default mode network (DMN) defined by the anterior medial PFC, posterior cingulate cortex (PCC) and angular gyrus has consistently demonstrated altered connectivity in depression[80]. The normal functioning of the DMN has been associated with self-referential processes, which may be maladaptively heightened in patients with depression[81]. Processes such as maladaptive rumination that are associated with depression, and involve a repetitive reflection of negative thoughts and emotions[82], are associated with hyper connectivity of the DMN both in depressed patients and healthy subjects [83].

It is likely that a simple linear relationship between increased or decreased connectivity in the DMN being correlated to depression and antidepressant response is over-simplified, and instead antidepressant therapies may work to reconfigure the default mode towards healthier patterns. In that vein, antidepressants have been found to affect and normalize altered DMN connectivity. In a study of healthy volunteers a two week administration of the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine was found to reduce default mode connectivity in healthy individuals during rest[84]. In a study of 41 patients with dysthymic disorder, a depressive disorder similar to MDD, who were found to have alteration of DMN activity compared to normal controls, 10 wk of treatment with duloxetine was found to normalize function in the DMN, compared to placebo which had no such effect[85]. Ketamine has also been associated with circuit level changes in the DMN. In a randomized, placebo-controlled, double-blind, crossover study in healthy subjects, ketamine was found to decrease functional connectivity of the DMN to the dmPFC [86]. A different study comparing HCs with patients with MDD measured functional connectivity at baseline and at 2 and 10 d after ketamine infusion. In subjects with MDD, connectivity between the insula and the DMN was normalized compared with HCs 2 d post ketamine infusion. This change was reversed after 10 d, a typical time course when the effects of ketamine begin to diminish and did not appear in either of the placebo scans, indicating this effect was an important aspect of the antidepressant function of ketamine[87].

Serotonergic psychedelics clearly alter DMN function and connectivity. A number of studies using LSD[88,89], psilocybin[90-92] and ayahuasca[93-95] have observed changes in functional connectivity of the DMN, and a common finding is an acute decrease in the integrity of the DMN. There are few studies that have looked at longer-term changes in DMN activity or connectivity. However, one study showed that in patients with depression treated with psilocybin, DMN integrity has been observed to increase or normalize in the post-acute period (1-d post-dose) accompanied by improvements in mood, and DMN normalization was predictive of treatment response at five weeks[96]. It is striking that in the early studies serotonergic psychedelics seem to have longer lasting treatment response than typically seen in ketamine studies, although clearly more evidence is required.

CHANGES IN BRAIN VOLUME ASSOCIATED WITH ANTIDEPRESSANTS AND PSYCHEDELIC AGENTS

Depression and antidepressant treatment have also been associated with neuroplastic changes at the volumetric level. One area that has been heavily implicated in being involved in depression is the hippocampus. Reductions of hippocampal volume have been seen in cynomolgus monkeys and in mice[46], and in humans reduction of hippocampal volume is one of the most common brain changes associated with depression and chronic stress[97,98]. The hippocampus (and medial temporal lobe) is a key part of the human default-mode-network, and stress-induced alterations in this structure may contribute to some of the network-changes observed above. Other consistently reported grey matter abnormalities associated with depression in humans include decreased volumes of the cingulate cortex, the PFC, the orbitofrontal cortex, amygdala, and the basal ganglia[99]. White matter lesions have also been demonstrated in depression and have been demonstrated as being especially prominent in late-life depression[100].

Amazingly, antidepressants have been shown to normalize hippocampal volume. One study found increased right hippocampal volumes in female responders compared to non-responders after eight weeks of treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine[101]. Other studies have demonstrated that patients treated with antidepressants who do not remit have lower bilateral hippocampal volumes at baseline and follow-up compared to remitted patients[102], though not all studies have found this relationship[103]. Studies investigating the effect of ketamine on structural brain changes are limited, although one study investigating the use of repeated ketamine treatment in patients with MDD observed increases in the volumes of the amygdala and hippocampus after just 6 ketamine infusions[104]. Studies on structural changes associated with serotonergic psychedelics are even more limited particularly with regards to humans with depression. However, in rodent models of trace fear conditioning, mice injected with low doses of psilocybin exhibited faster extinguishing of fear conditioning and an increased number of cells in the hippocampus compared to mice injected with saline or high dose psilocybin[105]. In non-depressed patients, one study found that 22 regular users of ayahuasca had thinning in the PCC and noted that cortical thickness values in the PCC were inversely correlated with personality traits measuring religiousness, transpersonal feelings and spirituality[106].

PSYCHOLOGICAL CHANGES ASSOCIATED WITH DEPRESSION, ANTIDEPRESSANTS AND PSYCHEDELIC FUNCTION

Plasticity can also relate to psychological changes in emotional, self, and social processing, which all play an important role in depression and antidepressant responses. Several studies have demonstrated that individuals with MDD demonstrate a bias towards negative emotional information compared to HCs[107,108]. Depression is also associated with perseverative negative ruminations[109]. Depression can also affect social processing, and has been associated with diminished desire for socialization, increased sensitivity to rejection, reduced cooperativeness, and impairment in understanding how others are feeling[110].

Antidepressants have been associated with changes in emotional processing[111], including changes in positive emotional recall with SSRIs and SNRIs in healthy volunteers, and changes in recognition of emotional facial expression, with the SSRI citalopram and the SNRI reboxetine reducing the identification of the negative facial expressions of harm and fear[112]. Ketamine may also lead to changes in these psychological processes. In a double-blind, placebo-controlled crossover study of 33 individuals with treatment-resistant MDD and 24 HCs, participants received ketamine and placebo infusions 2 wk apart, and functional magnetic resonance imaging scans were conducted at baseline and 2 days after each infusion during an attentional bias dot probe task with emotional face stimuli using "happy", "angry" or "neutral" faces across multiple time points. Ketamine infusion was found to have opposite effects on brain activation in regions associated with emotional processing in MDD *vs* HC participants, and in participants with MDD led to similar brain activity as HCs after placebo suggesting a possible "normalizing" effect on emotional processing in patients with MDD[113].

Serotonergic psychedelics also result in sustained and profound changes in emotional processing and sociability. LSD and psilocybin have been observed to decrease the recognition of negative facial expressions in healthy participants[114, 115]. Another study of healthy participants looking at changes in affect one week and one month after administration of psilocybin observed that negative affect decreased 1 wk after administration of psilocybin and positive affect increased, and while the changes in negative affect normalized after 1 mo, changes in positive affect persisted [116]. Beyond this, other unique psychological changes have been associated with serotonergic psychedelics, including a shift from a sense of disconnection from oneself, others, and the world to a sense of connection, and from avoidance of emotion to acceptance[117]. Both LSD and psilocybin have also been shown to acutely increase emotional empathy, and LSD was found to increase prosocial behavior on a social value orientation test. One unique property of serotonergic psychedelics is the experience of ego-dissolution which may occur during peak psychedelic experiences or "mystical experiences" where one experiences a loosening sense of boundaries between themselves and the world and a sense of unity and interconnectedness. It is possible that this subjective experience may in part account for shifting the relationship to one's sense of self and towards one's sense of connection with others. It

is interesting that the quality of the subjective "peak experience" has been associated with therapeutic efficacy[118]. Indeed, one plausible explanation for why serotonergic psychedelic agents are effective is that they evoke psychological experiences acutely while (at a molecular/cellular level) activating mechanisms of plasticity that help to engrain these experiences in long-term memory.

CONCLUSION

There is increasing evidence that psychedelic agents may induce rapid synaptic plasticity, and that this plasticity may be a key mechanism by which they can exert long-term antidepressant effects. However, it is important to note that plasticity is not, by itself, an inherently "anti-depressant" action. Indeed, as reviewed above, depression, anxiety and PTSD can, themselves, be caused or exacerbated by maladaptive forms of plasticity. Thus, the particular locus of this plasticity (neuronal sub-type, brain region, large-scale brain network) is important in understanding how such drugs cure depression. Psychedelic agents affect the brain in very different ways than ketamine (both when measured at the level of single units and local field potentials, or fMRI). However, longer-term changes in default-mode-network function may be a common endpoint linking both ketamine and psychedelic drugs in explaining antidepressant function of both agents. It is also vitally important to consider the psychedelic experience itself. The psychedelic experience has been described by some participants as being among the most meaningful or spiritually significant experiences of their lives[119]. If psychedelic agents produce these altered brain states, while simultaneously activating molecular/cellular cascades linked with plasticity, it could, indeed, provide a completely unique way of rapidly consolidating the effects of the experience for long-term retention. Trauma provides an example of how a single event, linked to mechanisms of plasticity, can cause long-term detrimental effects on brain and behavior[120]. Serotonergic psychedelics may well be the opposite — a pharmacologically-induced state of altered consciousness in which experiences are consolidated due to heightened mechanisms of synaptic plasticity.

Many questions remain. First, the question of to what extent neuroplasticity plays a role in depression. MDD is a complex disorder, and numerous factors play a role in its development including genetic, epigenetic, developmental, inflammatory, endocrine and psychological changes. A complete model of depression would account for how these various factors interlink to lead to the ultimate outcome of depression. Similarly, the question exists of to what extent neuroplasticity plays a role in the therapeutic effect of serotonergic psychedelics. The question also remains as to whether the therapeutic effect of serotonergic psychedelics is dissociable from the drugs subjective effects. While it is likely that neuroplasticity plays a role in the antidepressant treatment response of serotonergic psychedelics, further research is warranted to better characterize the other factors that play a role.

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World Journal of Psychiatry

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World J Psychiatr 2021 June 19; 11(6): 215-221

DOI: 10.5498/wjp.v11.i6.215

ISSN 2220-3206 (online)

MINIREVIEWS

Intimate partner violence: A loop of abuse, depression and victimization

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Conflict-of-interest statement: Authors declare no conflict of interest.

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Abstract

Intimate partner violence has been recognized as a serious public health issue. Exposure to violence contributes to the genesis of, and exacerbates, mental health conditions, and existing mental health problems increase vulnerability to partner violence, a loop that imprisons victims and perpetuates the abuse. A recently described phenomenon is when male violence against females occurs within intimate relationships during youth, and it is termed adolescent or teen dating violence. In this narrative review, factors associated with intimate partner violence and consequences of exposure of children to parental domestic violence are discussed, along with possible intensification of violence against women with the spread of coronavirus disease 2019 pandemic and subsequent lockdown. Intervention programs with a multicomponent approach involving many health care settings and research have a pivotal role in developing additional strategies for addressing violence and to provide tailored interventions to victims. Prevention policy with a particular attention on healthy child and adolescent development is mandatory in the struggle against all forms of violence.

Key Words: Intimate partner violence; Women; Depression; Abuse; COVID-19; Personalized medicine

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 31, 2020
Peer-review started: December 31, 2020
First decision: April 21, 2021
Revised: April 25, 2021
Accepted: May 17, 2021
Article in press: May 17, 2021
Published online: June 19, 2021

P-Reviewer: Zafrakas M
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Li JH



Core Tip: Intimate partner violence represents a serious public health issue. Exposure to violence contributes to the genesis of, and exacerbates, mental health conditions, and existing mental health problems increase vulnerability to partner violence. A recently described phenomenon is when male violence against females occurs within intimate relationships during youth, and it is termed adolescent or teen dating violence. Coronavirus disease 2019 pandemic is causing a tremendous impact on women's possible exposure to violence. Possible interventions against violence are discussed.

Citation: Mazza M, Marano G, del Castillo AG, Chieffo D, Monti L, Janiri D, Moccia L, Sani G. Intimate partner violence: A loop of abuse, depression and victimization. *World J Psychiatr* 2021; 11(6): 215-221
URL: https://www.wjgnet.com/2220-3206/full/v11/i6/215.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i6.215

INTRODUCTION

Intimate partner violence is described as physical violence, sexual violence, stalking, or psychological aggression by a current or former intimate partner. It represents a serious public health issue. It has been estimated that more than 30% of women in the United States have experienced intimate partner violence, and it represents the leading cause of homicide death for women. Prevalence is higher among young women (18 to 24 years of age), among racial and ethnic minority groups, and among people with mental and physical disabilities[1]. Psychological violence is estimated to be the most common subtype of intimate partner violence (compared to physical and sexual violence) in the United States and Europe[2].

In women of reproductive age, intimate partner violence has been linked with poor reproductive health and poor sexual health (unintended pregnancy and sexually transmitted infections) and heightened risks of obstetrical and gynecologic complications (pregnancy-associated death, preterm birth, low birth weight) and represents a risk factor for peripartum depression and substance abuse[1]. There are specific physical injuries in women that can be considered as indicators of intimate partner violence: Contusions, lacerations, and fractures (especially in the head, neck and face) and are frequently reported by patients as domestic accidents. Partner violence has been associated with many mental health consequences: Depression, anxiety, post-traumatic stress disorder, eating disorders, suicidal behavior, alcohol or drug abuse, sexual problems, problems with concentration, somatization, social, educational, or occupational difficulties, as well as feelings of blame and guilt or reproach. It is also linked to several and often disabling physical health problems (chronic pain, gastrointestinal problems, sexually transmitted infections, traumatic brain injury, cardiovascular diseases).

Exposure to violence can contribute on one side to the genesis of psychopathological conditions or can exacerbate mental health conditions, but on the other side existing mental health problems can increase vulnerability and predisposition to partner violence.

It has been estimated that emotional violence is the most common form of intimate partner violence across all continents worldwide[3]. Factors associated with intimate partner violence originate from multiple levels: Individual, relationship, community, and societal level[4]. Subjects who are at greater risk of experiencing intimate partner violence more likely come from a lower education background and poorer socio-economic status (with difficulty of access to resources and greater acceptance towards violence), have a history or a current substance abuse, and have been exposed to prior abuse or violence (with a history of abuse reinforcing the normative nature of violence and developing violence-condoning attitude). For example, many immigrant women have to cope with issues regarding their cultural integration into another society while at the same time concurrently feeling related and profoundly bounded by cultures and traditions from their countries of origin. Dependence on one's partner, difficulties in language proficiency, financial problems, lack of social support, and uncertain legal status can leave these subjects feeling fragile and socially isolated and can prevent them from seeking assistance; besides, women linked to particular cultural backgrounds may refuse to acknowledge certain acts and behaviors as abusive due to

beliefs and traditions regarding familial obligations and culturally prescribed gender roles[5].

People with mental illness may have a heightened risk of becoming victims of domestic violence and can be reluctant to disclose abuse. On the other hand, mental ill-health can also be a consequence of victimization and can involve post-traumatic stress disorder, depression, suicidality, and alcohol or substance misuse: Physical sequalae of abuse are added to psychological morbidity[6].

EXPOSURE OF CHILDREN TO PARENTAL DOMESTIC VIOLENCE

It has been outlined by recent research that the presence of intimate partner violence often compromises a child's attachment to primary caregivers, which results in an additional risk factor for social, emotional, and psychological impairment[7]. A child can be exposed to domestic violence also through the awareness that violence occurs between parents, regardless of whether the child directly witnesses it. Infancy is a critical period of developing a secure attachment, and infants spend most of the time with caregivers, in a relationship of close proximity to them and high and obliged dependence from them; in addition, younger children have not completely strengthened the cognitive ability to discern between intimate partner violence as a threat to caregiver or to the self. As a consequence, the situation of violence in the household can indirectly impact on the child because it compromises the caregiving system in the parent. The presence of intimate partner violence increases a child's risk of developing a wide variety of negative outcomes (internalizing symptoms, externalizing behaviors, problems with perceptual and cognitive functioning, academic difficulties, interpersonal difficulties). Possible consequences can be affected by the child's age, relationships with other caregivers, and period of exposure to violence.

Violence against young girls causes physical and psychological effects, which can manifest as mild anxiety symptoms, apprehension, flashbacks, or feeling ashamed or worried to more severe anxiety signs, including a variety of sleep or eating disorders, post-traumatic symptoms, and even thoughts of self-harm and suicide. The inaction of a valid support system may further worsen this complex situation[8].

Children exposed to parental domestic violence are predisposed to physical and mental health disorders and are subjected to an increased risk of become a victim or a perpetrator of intimate partner violence in adolescence and adulthood[9]. Besides, adverse childhood experiences, such as child abuse, maltreatment, substance abuse in the household, incarceration of household members, and emotional or physical neglect, have long-term consequences with poorer physical, mental, individual behavioral, and social/interactional outcomes: The larger the number of adverse childhood experiences, the higher the odds of worst physical and mental health outcomes, including heart disease, stroke, asthma, diabetes, and mental distress[10]. Adolescence is a critical developmental period characterized by puberty, progressive autonomy from parents and family, changes in social relationships, and often the beginning of romantic relationships. Child sexual abuse, child physical abuse, witnessing parental intimate partner violence, exposure to school-related violence (*e.g.*, bullying), and community violence (*e.g.*, racism or discrimination) during childhood are potentially related to future intimate partner violence. Recently, it has been demonstrated that adverse childhood experiences in adolescence are predictive of interpersonal violence 15 years later[10].

Teen dating violence

When male violence against females occurs within intimate relationships during youth, it is termed adolescent or teen dating violence, occurring in individuals aged 10-24 years, including early, middle, and late adolescence, and described as physical, sexual, or psychological/emotional abuse, comprising threats, towards a dating partner. Six forms of teen dating violence have been assessed: Threatening behaviors, verbal/emotional abuse, relational abuse, physical abuse, sexual abuse, and stalking.

The cultivation of emotional relationships during adolescence are pivotal to the progressive growth of interpersonal communication skills, autonomy, and self-perceived competence, but together with affective and behavioral vulnerability experienced during adolescence, a variety of individual, social, and community risk factors may favor the emergence of adolescent dating violence[11]. Victims of teen dating violence may develop adverse health outcomes such as increased sexual risk behaviors, suicidality, unhealthy behaviors (*e.g.*, lack of physical activity and negative weight-controlling behaviors), inauspicious mental health outcomes, substance use,

injuries, victimization, and death. Additionally, it is common for adolescents who experience dating violence to struggle with their academics, drop out of school, or skip school to avoid seeing their partner.

Risk factors for perpetration of adolescent dating violence seem to be a history of experiencing, witnessing, and/or initiating abuse within the home, school, and community; childhood trauma in the form of physical and emotional abuse or neglect (due to personality anxiety traits formed during childhood, so that the individual feels a lack of security in the relationship and worries about being left by the partner); sexism and gender roles present in society; bullying; developing and formulating ineffective interpersonal communication and conflict resolutions skills during adolescence; alcohol or substance use during adolescence; attachment insecurities (anxiety and avoidance) expressed as anger, hostility, aggression, and emotional dysregulation[12]. Recent research suggests that there are multiple form of adolescent dating violence and that males may be victimized at similar rates as females[13]. Increasingly high rates of technology usage, as well as diffusion of apps and social media platforms, has created more opportunities for cyber teen violence dating (typically people who are no longer with their dating partner perpetrate this form of violence against an ex-partner).

Abusive behavior in adolescent dating relationships is associated with a risk of intimate partner violence later in adulthood[14].

Violence during coronavirus disease 2019 pandemic

Coronavirus disease 2019 (COVID-19) has had a dreadful impact on the world's economy, and women are forced to take on additional risks as they are already disadvantaged and vulnerable, especially in rural and remote settings[8]. Sexuality suffers because it has to deal with the arrogance of a death drive rekindled by the current pandemic condition. A life in which less libido is exchanged stably than one would like can become unbearable. But the libido, in the forms of stasis and engorgement, can turn, in the unconscious, into anguish and give rise to internal conflicts that inevitably end up resulting in the relationship with the other[15]. As the COVID-19 pandemic has intensified, its effects diversified by gender have begun to gain attention[16]. During the institutional lockdown, victims of domestic violence were required to remain closed with partners and without help or support: In such scenario there is a great chance that abusive situations can further aggravate, with a possible increase of domestic homicides or murder-suicides or deviant behaviors towards children. Increased concerns about domestic violence have been expressed in many countries. The reasons for this include social isolation, exposure to economic and psychological stressors, increase in negative coping mechanisms (such as alcohol or drugs misuse), and inability to access usual health and social services[6]. School closure due to lockdown can potentiate the risk for children to witness violence, exploitation, and abuse at home and away from help[8].

As the outbreak of COVID-19 has developed, referral rates to mental health and psychology services have declined, despite a likely increase in psychological distress, victimization, and mental illness. It is well-known that intimate partner violence has short-term and long-term effects on physical and mental-health of affected subjects and in particular might increase the risk of cardiovascular disease in women, by indirect (chronic inflammation or dysregulation of the hypothalamic pituitary axis as a consequence of chronic stress) and indirect pathways (coping strategies used by victims of abuse to deal with stress, such as smoking and overeating, and higher incidence of depressive disorders correlated to chronically elevated levels of cortisol, catecholamines, and inflammatory markers, all of which promote the development and progression of cardiovascular disease)[17].

Psychological distress linked with the pandemic itself, arising in response to fears about personal and familial infection as well as the sequelae of social distancing and quarantine measures, add worry about possible consequences of intimate partner violence during this global pandemic.

Particularly during the COVID-19 pandemic, programs are necessary to provide funding sources to guarantee telephone or remote counseling services or psychological assistance hotlines to manage and attempt to prevent crisis situations[18,19]. The use of mobile health and telemedicine to support safely subjects experiencing violence must be urgently improved, together with other strategies to reach women at risk in settings where access to mobile phones or the internet is limited or completely lacking. We must learn lessons from the past epidemics and also from the present about errors and defeats to recognize and address gender related effects of outbreaks[16].

Prevention and management of the violence against women of all ages should be expected and potentiated as a pivotal service in the COVID-19 response plan.

CONCLUSION

Possible interventions against violence

Lifetime and current intimate partner violence is common and unacceptably high. It has been outlined that approximately 1 in 4 women becomes a victim of violence at some point in their life regardless of their age, economic status, or ethnicity. Domestic violence against women is a well-recognized health concern and has serious negative impact on women's lives. It is important to stress the fact that most of the factors associated with violence against women are preventable. Studies assessing screening and interventions practice in primary care services for women who experience intimate partner violence have demonstrated that clinical programs can mitigate the risk of subsequent violence[20]. In addition, interventional studies have stressed that gender-norms transformation through behavioral change and communication focused program can promote gender equality norm and avert domestic violence against women[21].

Intimate partner violence is often not obvious, and patients may present with nonspecific signs and symptoms. Clinicians must be aware of the red flags of domestic violence and incorporate the principles of trauma-informed care into their practice. This means asking about violence or risk of violence when it is safe and appropriate, in a private discussion and in a compassionate and nonjudgmental way, discussing needs, preferences, and immediate options. It is necessary to support the subject's autonomy, provide emotional and practical support, and personalize responses and possible solutions to the individual patient[22].

For pregnant women suspected or known to be exposed to partner violence, it is mandatory to consider a pregnancy high-risk and to provide prenatal assessment and counseling for the mother and home-visitation programs in the child's first years. Screening in primary care for mental health disorders such as depression or anxiety should reasonably include an inquiry about current and previous intimate partner violence. In parallel, current or past intimate partner violence should be appropriately included in the differential diagnosis of many medical and behavioral health conditions, particularly in women[1]. It should be taken into account the fact that violence victims may not disclose their experience immediately but in the context of multiple queries and a trusting relationship. It results important that a multicomponent approach involving many health care settings, training of staff, clinical specific tools of assessment (including multiple violence domains: Physical, sexual, emotional/psychological), established workflows, connection to follow-up social services, and legal services can be dedicated and promoted to improve the prevention and response and care to the problem of intimate partner violence and its serious consequences. It has been observed that women have the tendency to remain with violent partners due to a variety of reasons, including social norms, worry for children, and economic issues. Immigrant women require a specific culturally-tailored approach and may need specific advocacy and interventions that also focus on financial abuse and are finalized to economic empowerment, including individual mental health counseling (when the shame and stigma associated to intimate partner violence in many ethnic communities increase the reluctance to discuss in groups) and services provided in community member's native language or in intervention delivery settings (shared community environments including churches, mosques, temples)[5].

Interventions integrating legal framework and programs that focus on transformation of traditional gender-norms are of great importance in order to prevent violence against women of all ages. There is an increasing need of intervention programs and techniques to reduce violence among offenders (group therapy or counseling aimed to work on impulsive and angry behavior or inability to control emotions) with a particular focus on trauma and substance abuse[23]. Since it has been observed that men with mental health problems (in particular depression, anxiety, alcohol or drug use disorder, attention deficit hyperactivity disorder, personality disorders) carry a higher probability to perpetrate domestic violence against women, treatment for any co-existing mental illness and in particular substance abuse or misuse should be prioritized to reduce risk[24].

Also, research has a pivotal role in developing additional strategies for addressing violence and to provide personalized interventions to victims. For example, qualitative studies exploring the emotional impacts of intimate partner sexual violence on women

Table 1 Proposed interventions against intimate partner violence

No.	
1	Clinical routine screening for indicators of intimate partner violence
2	Prenatal assessment and counseling for pregnant women suspected or known to be exposed to violence and home-visitation programs
3	Culturally tailored specific approach for immigrant women victims of violence
4	Intervention tecniques to reduce violence among offenders
5	Implementation of research aimed to develop additional strategies for addressing interpersonal violence
6	During COVID-19 pandemic, enhancement of telephone or remote counseling services or psychological assistance hotlines to manage crisis situations
7	Specific programs for prevention of domestic violence with a particular attention on healthy child and adolescent development

COVID-19: Coronavirus disease 2019.

are scarce. Understanding should be deepened of the so-called invisible impacts of violence, described as the emotional repercussions (sense of powerlessness, helplessness, shame, ongoing fear of men) that are difficult to quantify and measure but may be a trigger for mental health outcomes, such as post-traumatic stress disorder, anxiety, and depression[25]. Research can guide attachment- and family-based interventions for families impacted by interpersonal violence. Besides, there is an urgent need for rigorous research to understand better which interventions are most effective and tailored for ethnic minority populations.

Last but not least, prevention is mandatory: Interventions focusing on community and domestic health and violence prevention and, focusing on high-risk and disadvantaged socio-economic groups (such as institutionalized children or adolescents), with a particular attention on healthy child and adolescent development, may greatly contribute to lower intimate partner violence victimization in adulthood by correcting attitudes on violence and improving help-seeking behavior (Table 1).

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 June 19; 11(6): 222-231

DOI: 10.5498/wjp.v11.i6.222

ISSN 2220-3206 (online)

MINIREVIEWS

Brain reward circuitry: The overlapping neurobiology of trauma and substance use disorders

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Author contributions: Novakovic V conceived of the manuscript topic; all authors assisted with the literature review; Michaels TI and Stone E wrote a large portion of the manuscript although all authors contributed to the writing process with specific subsections written by Novakovic V, Stone E and Singal S; Barkin RL and Barkin S provided significant guidance as well as edits and revisions to the manuscript; Michaels TI and Stone E revised the manuscript prior to publication.

Conflict-of-interest statement: The authors have declared that no competing interest exists.

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Abstract

Mental health symptoms secondary to trauma exposure and substance use disorders (SUDs) co-occur frequently in both clinical and community samples. The possibility of a shared aetiology remains an important question in translational neuroscience. Advancements in genetics, basic science, and neuroimaging have led to an improved understanding of the neural basis of these disorders, their frequent comorbidity and high rates of relapse remain a clinical challenge. This project aimed to conduct a review of the field's current understanding regarding the neural circuitry underlying posttraumatic stress disorder and SUD. A comprehensive review was conducted of available published literature regarding the shared neurobiology of these disorders, and is summarized in detail, including evidence from both animal and clinical studies. Upon summarizing the relevant literature, this review puts forth a hypothesis related to their shared neurobiology within the context of fear processing and reward cues. It provides an overview of brain reward circuitry and its relation to the neurobiology, symptomology, and phenomenology of trauma and substance use. This review provides clinical insights and implications of the proposed theory, including the potential development of novel pharmacological and therapeutic treatments to address this shared neurobiology. Limitations and extensions of this theory are discussed to provide future directions and insights for this shared phenomena.

Key Words: Posttraumatic stress disorder; Substance abuse; Reward circuitry; Mesolimbic;

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 28, 2021
Peer-review started: February 28, 2021
First decision: April 6, 2021
Revised: April 14, 2021
Accepted: May 20, 2021
Article in press: May 20, 2021
Published online: June 19, 2021

P-Reviewer: Vyshka G
S-Editor: Gao CC
L-Editor: A
P-Editor: Xing YX

Neurobiology

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Core Tip: Traumatic stress disorders and substance use disorders are highly co-morbid in community and clinical samples. Recent findings from basic and clinical neuroscience support a shared neural basis of these disorders, specifically related to the processing of fear and reward cues. Understanding the overlapping neurobiology of these disorders will improve our understanding of disease aetiology and improve prevention and treatment efforts.

Citation: Michaels TI, Stone E, Singal S, Novakovic V, Barkin RL, Barkin S. Brain reward circuitry: The overlapping neurobiology of trauma and substance use disorders. *World J Psychiatr* 2021; 11(6): 222-231
URL: https://www.wjgnet.com/2220-3206/full/v11/i6/222.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i6.222

INTRODUCTION

Research focused on trauma and posttraumatic stress disorder (PTSD) dates back to 1889, when Pierre Janet, a prominent French psychiatrist, published *L'Automatisme Psychologique*, an early attempt to describe how the mind processes traumatic events [1]. Janet argued that patients suffering from dissociation and hysteria had unresolved traumatic memories and that this subconscious experience was routed in the physical effects of past negative experiences. When an individual experiences a traumatic event, they are overwhelmed with intensely negative emotions and are unable to accurately process and remember details surrounding the event[2]. The traumatic experience dissociates from conscious awareness. Janet believed that the individual would relive the memory of the trauma in fragmented pieces, such as emotional states, somatic conditions, visual images, or behavioral re-enactments. Janet was the first to identify dissociation as the crucial psychological technique involved in a variety of post-traumatic symptoms[1].

Decades of research on understanding the psychological and biological effects of trauma have provided support for many of Janet's early observation[1]. Psychological distress following a traumatic event can manifest through a variety of symptoms including anxiety and exaggerated fear as well as anhedonia, dysphoria, anger, aggression, or dissociation[3]. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) provides a description of seven different diagnoses which all relate to exposure to a prominent or stressful event, the most prevalent of these diagnoses are Acute Stress Disorder and PTSD. Criteria for PTSD include direct exposure to or indirect witnessing of a traumatic or stressful event, as well as the presence of intrusive symptoms, negative mood, dissociation, avoidance and/or arousal. These symptoms must cause clinically significant distress or impairment and must not be attributable to the effects of a substance, a medical condition, or a brief psychotic disorder[3]. Patients with PTSD must also display at least one or more symptom across each category (intrusive, avoidance, negative alterations in cognition and mood, alterations in arousal and reactivity). Interpersonal trauma is one of the most common criteria A events and is more likely to lead to poorer functional outcomes[3].

Given the diversity and complexity of individual responses to trauma, it has been difficult to fully understand the neurobiological substrates involved in PTSD. The majority of basic neuroscience and neuroimaging research on PTSD has focused primarily on two areas; the effect of stress on sympathetic nervous system functioning and the impact of trauma on frontal striatal brain circuitry[4]. Although such research has begun to shed light on the adverse neurobiological effects of repeated stress, many patients continue to suffer from the effects of trauma and are resistant to empirically validated treatments for PTSD[5]. An emerging area of research that may help to further elucidate the neurobiological mechanism of trauma relates to the important role of reward circuitry in translational models of PTSD. After providing an overview

of animal and clinical research on the biological effects of PTSD, this article will review recent research that suggests an important role for the brain's reward pathway in understanding the neurobiological effects of complex trauma.

THE PHYSIOLOGY AND NEUROBIOLOGY OF PTSD

The human stress response and PTSD

During stress, the sympathetic nervous system prepares an individual for action while the pituitary-adrenocortical system dampens initial physiological aspects of arousal [6]. The hypothalamic (HPA) axis releases corticotrophin releasing factor (CRF) which stimulates the release of cortisol from the adrenal cortex, and increases the release of catecholamine neurotransmitters within several regions of the brain[7]. Catecholamines have an integral role in the adaptive response to stress through the breakdown of glycogen, the suppression of the insulin release, and increased functioning of the cardiovascular system[6]. Increased levels of norepinephrine (NE) and epinephrine (EPI) during stress result in increased neuronal activity in limbic areas such as the amygdala, and hypothalamus, and decreased activation of cortical areas involved in higher-order cognitive functioning[8].

For individuals at risk for developing PTSD, traumatic experiences can alter the normal functioning of the sympathetic nervous system. Many of the core symptoms of PTSD reflect a state of hyperarousal including exaggerated startle response, initiating and maintaining sleep and poor concentration[9]. Patients with PTSD demonstrate exaggerated sympathetic nervous system responses including tachycardia and skin conductance during acute stress and increased sensitivity of the HPA axis[10]. Compared to healthy controls, patients with PTSD have reduced baseline cortisol levels, and increased levels of CRF[11]. Several studies have demonstrated that patients with PTSD have higher urinary secretion levels of NE, and EPI, compared to controls and that neurotransmitters levels correlate with the severity of self-reported PTSD symptoms[10,12]. Previous PTSD studies have reported related abnormalities in sensory processing including deficits in the P50 and P300 evoked potential component [13].

Abnormalities in HPA axis and neurotransmitter function can alter neural circuitry both structural and functional changes of, especially in brain circuits integral to affective and cognitive processing. While high levels of cortisol enhance the formation of emotional memories (mediated by the increased amygdala function) and facilitates fear conditioning, high levels of cortisol upon trauma exposure decreases hippocampus function, resulting in memory and learning deficits[14]. Structural changes occur as well; high levels of stress can result in dendritic hypertrophy of the prefrontal cortex (PFC), and dendritic remodeling of the amygdala[15].

Between stimulus and response

How does the brain process sensory information that may be perceived as a threat? LeDoux was among the first to demonstrate the underlying neural circuitry of fear (Figure 1) For example, imagine that a door slams shut in the middle of the night, waking you up from sleep. The initial sensory information about the threat is relayed to the thalamus and then quickly sent to the amygdala, activating the stress response and generates an immediate reaction. The body begins to sweat, a diaphoretic response that precipitates a rapid response. The hippocampus and PFC process contextual information about the stimulus by providing reasoning (perhaps it was a windy day) and episodic memory (a slamming door has never caused you any harm) that dampens the stress response and allow an individual to relax, returning to baseline. The signal from the thalamus to the amygdala is rapid, while signals from the hippocampus and PFC are transmitted with less velocity[16]. Recent translational research has demonstrated how structural, chemical and functional differences in each of these brain areas evolve in the neurobiology of PTSD.

Given the role of intrusive memories in PTSD, many have speculated that hippocampal dysfunction is a critical component of the underlying neurobiology. The hippocampus has a high concentration of corticosteroid receptors that are involved in the termination of the stress response through the negative feedback of the HPA axis [17]. Both animal and human studies have demonstrated that high levels of stress can damage the hippocampus, resulting in memory impairments[18]. During an acute stress response, high levels of cortisol can diminish dendritic branching in the hippocampus while augmenting neurogenesis in the amygdala, enhancing the emotional salience of the event, but impairing memory functioning[15,19]. When

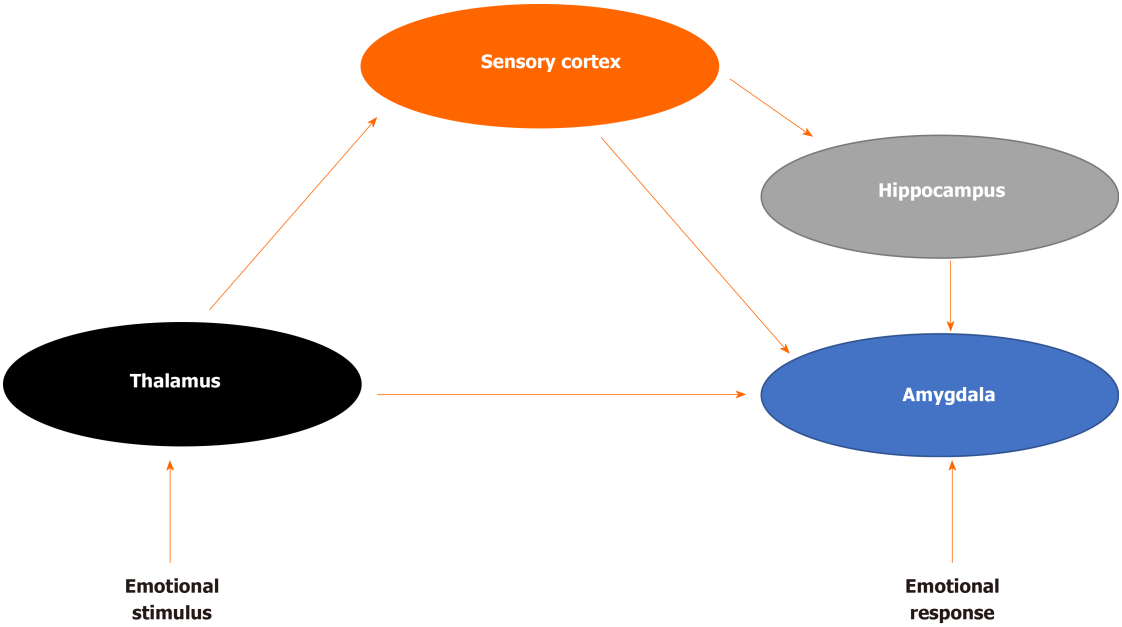


Figure 1 Fear brain circuitry.

compared with healthy controls, patients with PTSD demonstrate impairments in short-term memory and some studies (but not all) have demonstrated reduced hippocampal volumes in patients with PTSD[20]. Patients with PTSD often have difficulty describing details related to traumatic events and some studies have correlated hippocampal regional cerebral blood flow with PTSD symptom seve-rity [21,22].

The amygdala receives input from the thalamus as well as sensory processing regions of the neocortex, and transmits signals to autonomic brain structures, thereby playing a critical role in both the sympathetic and parasympathetic stress respo-nse[23, 24]. In human studies, the amygdala has been demonstrated to have a critical role in processing emotional stimuli, and in the formation of emotionally salient memories [25]. It also has a role in fear conditioning, whereby a neutral conditioned stimulus is associated with an unconditioned stressful stimulus. Exposure to the conditioned stimulus initiates the stress response, activates the amygdala, and engages the autonomic nervous system[26]. Lesion of the amygdala interrupts fear learning and the conditioned response in animals[27,28]. Human neuroimaging studies have confirmed the involvement of this region in fear learning, conditioning and extinction [29,30]. Compared to healthy controls, patients with PTSD demonstrate increased activation of the amygdala when presented with trauma-related cues, as well as when presented with unrelated affective stimuli[31,32]. Amygdala response in patients with PTSD has been found to correlate with self-reported symptom severity[33,34].

Alterations in prefrontal cortical (PFC) activity may help to link the role of memory impairment in PTSD as well as increased amygdala activation during the stress response[20]. In patients with PTSD, repeated exposure to trauma damages these neural structures. The ability to extinguish emotional memories involves the ventro-medial PFC as well as the amygdala while extinguishing conditioned fear involves the anterior cingulate cortex and the amygdala[24,35]. Activation of the medial PFC also occurs when inhibiting fearful responses or altering one's perception of a negative emotional event and therefore decreased functioning of the PFC may explain why patients with PTSD exhibit difficulties in extinguishing fearful memories[36,37].

COMORBIDITY OF PTSD AND SUBSTANCE USE DISORDERS

Clinical observations, case reports and epidemiological studies first suggested high rates of comorbidity between PTSD and substance use disorders (SUD), prompting translational research examining the possibility of overlapping neural mechanisms. Many studies have demonstrated a high comorbidity of PTSD with drug addiction in both clinical and community samples[38,39]. Approximately 36% to 50% of those that

meet criteria for SUD also meet criteria for lifetime PTSD, and those with PTSD predictably have a history of drug abuse or dependence[40]. Comorbidity of these disorders is associated with negative treatment outcomes, increased risk for chronic diseases, and poorer functionality[41]. Co-twin studies have also demonstrated a link between childhood trauma and the later development of SUD[42].

Robinson and Berridge[43] proposed a model of addiction that demonstrates how repeat drug use disrupts normal reward processing. The Incentive-Sensitization Theory postulates that although increased pleasure is initially an important part of addiction behavior, regular substance use increases an individual's sensitivity to drug cues, causing them to become hyper-responsive to drug cravings, even in the absence of pleasure[43]. This hyper-sensitization produces goal-directed behavior ("wanting") not only in the absence of subjective pleasure, but also in the absence of consciously being aware of "wanting". Recent research has supported this theory, demonstrated that substance use can alter brain reward circuitry[43].

BRAIN REWARD CIRCUITRY AND SUD

Data from several studies suggest that the reward circuit of the brain (the mesocortical dopamine pathway) provides a common molecular pathway with which to understand SUD. The mesolimbic pathway involves connections between the ventral tegmental area (VTA), the nucleus accumbens (NAc) in the ventral striatum, and the PFC. The mesolimbic dopamine reward circuit controls the reinforcing and rewarding effects related to food, sex, and social interaction[44]. Drug-induced adaptations in mesolimbic dopamine system (includes common adaptations to many different drugs) mediate changes in reward mechanisms that in part underlie addiction — including tolerance, dependence-withdrawal, sensitization, and relapse. Drug-induced adaptations include regulation of dopamine and opioid systems (mechanisms of tolerance and sensitization), regulation of glutamate systems (influences drug-related memories), upregulation of the cyclic adenosine monophosphate (cAMP) pathway, and transcription factor cAMP Response Element-Binding (CREB) protein, (mechanisms of drug tolerance, dependence, and withdrawal), structural changes in VTA neurons (influences drug tolerance), and structural changes in NAc neurons (influences drug sensitization)[45].

Many studies show that dopamine and accumbens neurons often become most active in anticipation of rewards, not during the reward phase, and also activated by the anticipation of aversive stimuli and events[46,47]. The role of the mesolimbic DA system is to increase the salience of stimuli and events associated with activation of the system. Stimuli are imbued with salience, making them "wanted" incentive stimuli. Alcaro *et al*[46] have theorized the role of the mesolimbic pathway as driving an organism toward "seeking" behaviors, searching to boost the salience of activities that are life-promoting while avoiding those that are harmful to survival. This proposed role is not only congruent with evidence of the importance of SUD, but also a mechanism that explains the connection of the VTA to the hippocampus, amygdala, and PFC, all of which have been implicated in the neurobiology of PTSD.

OVERLAPPING NEUROBIOLOGY OF PTSD AND SUD

Both animal models and clinical studies of PTSD have noted deficits in reward processing consistent with hypofunctionality of the mesolimbic pathway. Upon exposure to chronic stress, animal models demonstrate reduced striatal dopaminergic activity and decreased reward-seeking behavior that mimic symptoms of anhedonia experienced by PTSD patients[48]. Corral-Frias *et al*[49] utilized a novel animal model of PTSD to demonstrated that inactivation of the VTA can lead to long-term behavioral changes that mimic the clinical symptoms of PTSD. Inactivation of the VTA through either a dopamine antagonist or bilateral dissection can also lead to chronic changes in baseline VTA dopaminergic cell firing, demonstrating that trauma can lead to long-term alterations of the reward pathway. Evidence of deficits in the brain reward and reinforcement circuits in patients with PTSD also supports the involvement of the mesolimbic dopamine reward circuit[50,51]. In clinical studies, PTSD patients spend less time engaging in reward-seeking behavior compared to controls, report lower levels of reward expectation and are less satisfied with monetized rewards[52,53]. When compared to healthy controls, patients with PTSD demonstrate reduced bilateral striatal activation when responding to positive to reward gains and reported

significantly higher levels of motivational and social deficits[50]. Collectively, these findings suggest a strong overlap in the brain regions involved in both fear processing and addiction. In particular, the VTA, through its connections to the amygdala, hippocampus and PFC, may serve as the common substrate of this overlapping circuitry, explaining the high co-morbidity in PTSD and SUD.

Several rodent models provide converging evidence for the overlapping circuitry of these two disorders, including the dorsal and ventral subdivisions of medial PFC and their respectively outputs to the amygdala and NAc (Figure 2). The prelimbic (PL) cortex projects to the basal (BA) nucleus of the amygdala, which excites the central (CE) nucleus of the amygdala, thereby promoting the expression of conditioned fear [54]. The BA also receives excitatory input from lateral amygdala, which also drives the expression of conditioned fear. The infralimbic (IL) cortex, in contrast, excites a class of GABAergic inhibitory neurons (the intercalated cell masses) which inhibit the CE, thereby promoting extinction of the conditioned fear[55]. PL and IL control drug seeking *via* their differential projections to the core and shell subdivisions of the NAc. The PL projects to the core, which promotes the expression of drug-seeking behavior. The IL projects to the shell, which also promotes the expression of extinction[56].

Functional magnetic resonance imaging studies provide consistent support for similar networks in human studies of fear and addiction (Figure 3). The dorsal portion of the anterior cingulate cortex is associated with fear expression during conditioning behavioral tasks, and overlaps with proximal regions that are activated when SUD patients respond regarding their craving levels after exposure to cocaine-related cues [57-59]. These findings are congruent with results from positron emission tomography mapping of cerebral blood flow using 15O-labeled water[60]. The ventral medial PFC (vmPFC) is activated during fear extinction recall and during recall of addiction cues in individuals with SUD disorders[57,61]. During states of cocaine craving, the vmPFC is deactivated, suggesting a failure to engage extinction[54]. Collectively, these studies suggest that the vmPFC is homologous to rodent IL, whereas the dorsal regions of anterior cingulate cortex are homologous to rodent PL.

CONCLUSION

This review examined evidence in support of a shared neurological origin between PTSD and SUD, in an effort to explain the high rates of comorbidity. It is clear that abnormalities in the PFC and VTA are central to the pathology of both disorders. The VTA is negatively affected during trauma and stress, and results in a decrease of dopaminergic activity and a subsequent alteration in the reward pathway. The PFC is involved in drug seeking behavior as well as the extinction of fear conditioning, playing a role in both addiction and PTSD. This review did not examine the genetic vulnerabilities nor neurodevelopmental pathways that may confer increased risk for either or both disorders, and it remains an important question whether the shared biology reviewed here is due to more distal risk factors, or are a result of one disorder conferring increased risk for the other.

It is important to gain a better understanding of the connection between PTSD and SUD in order to develop improved treatments that target both disorders. Despite shared neurobiology, there are few treatment options that target both, although notably some do exist (*e.g.*, Seeking Safety). Yet many patients are not able to benefit from combined treatment interventions during the earlier stages of substance use recovery, and clinicians often struggle to determine the priority of treatment[62]. Many individuals diagnosed with comorbid PTSD-SUD believe that the outcomes of their disorders are interconnected, yet are not offered treatment for PTSD alongside SUD interventions[63].

Understanding comorbidity may also further prevention efforts, consistent with the "self-medication" hypothesis, as individuals with untreated trauma utilize substance as unhealthy coping mechanisms[64]. Earlier identification, access to care, and treatment of trauma across the lifespan is critical for intervening before the development of SUD or other maladaptive behaviours. Further research must leverage mechanisms between these two disorders, to ensure a more effective and efficient treatment option.

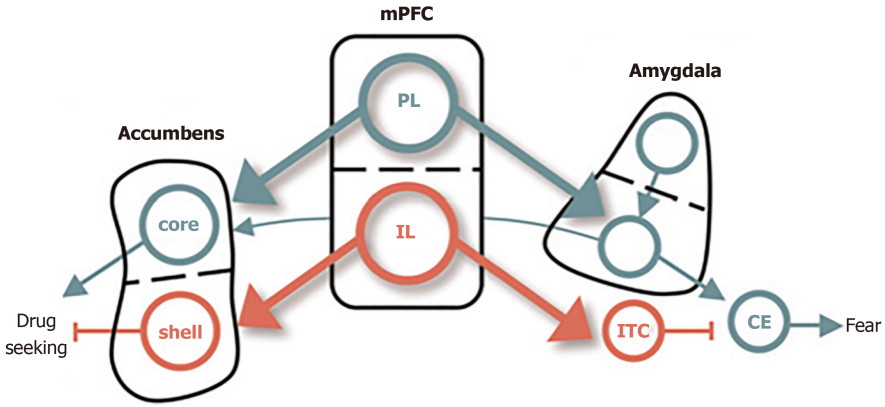


Figure 2 Conditioned fear in cocaine use. The dorsal and ventral subdivisions of medial prefrontal cortex are shown at the center, with their respective outputs to the amygdala controlling fear shown at right, and those to the nucleus accumbens, controlling cocaine, seeking shown at left. Green depicts pathways that activate fear and cocaine seeking. Red depicts pathways that inhibit fear and cocaine seeking[65]. Citation: Peters J, Kalivas PW, Quirk GJ. Extinction circuits for fear and addiction overlap in prefrontal cortex. *Learn Mem* 2009; 16(5): 279-288. Copyright ©Cold Spring Harbor Laboratory Press 2009. Published by Cold Spring Harbor Laboratory Press[65].

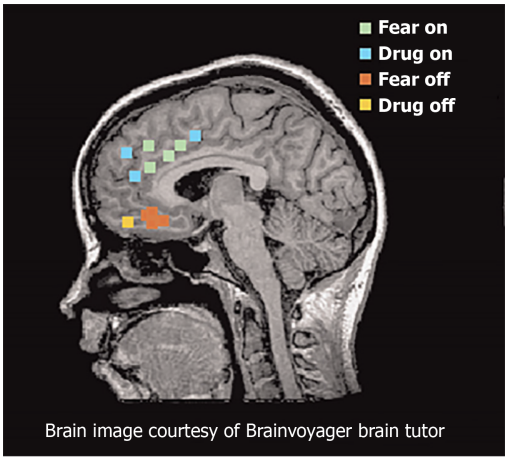


Figure 3 Functional magnetic resonance imaging and positron emission tomography studies of fear and addiction. Green dots represented human dorsal anterior cingulate cortex that correlated with fear expression functional magnetic resonance imaging[65]. Blue dots represent regions that correspond with drug cravings after exposure to cocaine-related cues. Red dots represent regions associated with fear extinction recall. Yellow dots represent regions activated during addiction-related cues. Citation: Peters J, Kalivas PW, Quirk GJ. Extinction circuits for fear and addiction overlap in prefrontal cortex. *Learn Mem* 2009; 16(5): 279-288. Copyright ©Brain Innovation 2009. Published by Cold Spring Harbor Laboratory Press[65].

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 June 19; 11(6): 232-241

DOI: 10.5498/wjp.v11.i6.232

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

COVID-19 impact on high school student's education and mental health: A cohort survey in China

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Author contributions: All authors contributed to the concept of this study; Baloch Z, Pan QW and Ma ZR designed the study; Ma WH and Baloch Z acquired and analyzed data; Baloch Z, Idris S and Pan QW wrote the manuscript; All the authors reviewed and approved the final manuscript.

Institutional review board statement: The Institutional Review Ethical Committee of Northwest Minzu University reviewed and approved the protocol used in this study.

Informed consent statement: Consent was obtained individually from each participant.

Conflict-of-interest statement: All authors declare no competing interests.

Data sharing statement: The datasets generated and analyzed during the current study are not publicly available due to the risk of compromising the individual privacy of participants, but are available from the corresponding

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Abstract

BACKGROUND

The ongoing coronavirus disease 2019 (COVID-19) pandemic and the universal implementation of control measures are fundamentally affecting every aspect of our society and daily lives.

AIM

To evaluate the prevalence of post-traumatic stress disorder symptoms and their associated factors as well as the effects and attitudes towards online education in Chinese high school students.

METHODS

A total of 883 students were included. The first, second and third-year students of a high school in Lanzhou, Gansu province of China were invited to participate in this study. They were requested to involve their parents to complete the survey together. A detailed questionnaire of 65 questions was designed and divided into five sections. The survey was anonymously conducted *via* WeChat, a Chinese multipurpose messaging, social media and mobile payment app.

RESULTS

Overall, 32.94% of students experienced post-traumatic stress disorder due to the COVID-19 epidemic. The majority of students (60.82%) felt that online education was not (10.76%) or less effective (50.06%) in terms of gaining knowledge and improving practical and communications skills. Correlation analysis revealed that the class level, residential background and whether living with parents were

significantly linked with the effectiveness and satisfaction of the online education system. Of the final year students, 74.2% said that the COVID-19 outbreak has negatively affected their preparation for the college entrance exam, and 68% of students felt that this outbreak increased psychological pressure for their college entrance examination preparation. In case of having COVID-19 symptoms during the exam, 50.7%, 13.3%, and 10.2% would notify the proctor, teacher and parents, respectively.

CONCLUSION

We found a high prevalence rate of post-traumatic stress disorder symptoms in high school students. Thus, our results call for urgent attention from both government and schools to implement effective interventions to cope with the psychological effects and the disturbance of education by COVID-19 on children.

Key Words: COVID-19; Post-traumatic stress disorder; Students; College entrance examination; China; Education

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Core Tip: This study evaluated the prevalence of post-traumatic stress disorder (PTSD) symptoms and their associated factors as well as the effects and attitudes towards online education in Chinese high school students. We found a high prevalence rate of post-traumatic stress disorder symptoms in high school students. Thus, our results call for urgent attention from both government and schools to implement effective interventions to cope with the psychological effects and the disturbance of education by coronavirus disease 2019 on children.

Citation: Ma ZR, Ma WH, Idris S, Pan QW, Baloch Z. COVID-19 impact on high school student's education and mental health: A cohort survey in China. *World J Psychiatr* 2021; 11(6): 232-241
URL: https://www.wjgnet.com/2220-3206/full/v11/i6/232.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i6.232

INTRODUCTION

The ongoing coronavirus disease 2019 (COVID-19) pandemic and the universal implementation of control measures are fundamentally affecting every aspect of our society and daily lives. School closure is one of the most important measures widely implemented worldwide. According to UNESCO's estimates, more than 190 countries have adopted nationwide school closures, resulting in roughly 90% of the global student population out of school and confined at home[1]. The classroom syllabus has been swiftly changed into an online education system. However, the education sector was not well-prepared to launch such large-scale online education programs. Thus, the effectiveness of this new education format and the effects on students remain largely uncertain.

According to epidemiological research after a traumatic event, about 5%-12% of individuals may develop post-traumatic stress disorder (PTSD) [2]. School closure, living in confinement and risk of the infection are creating anxiety and are affecting education, psychological health and well-being of students [1]. According to Chinese government estimates approximately 220 million teenagers were not allowed to go out during the COVID-19 epidemic in China. However, the consequences and the degrees of impact could vary among different levels of students.

In China, the schooling system includes primary school (6 years), junior middle school/secondary school (3 years) and senior middle school/ high school (3 years). Afterwards, students have the opportunity to continue to higher education by passing the college entrance examination, a nine-hour national higher education entrance exam. It is offered once a year and taken by around 10 million students annually. It is the sole determinant for admission to virtually all Chinese colleges and universities. Because of a limited amount of university spots available, it is an ultra-competitive

author on reasonable request.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Manuscript source: Unsolicited manuscript

Specialty type: Psychiatry

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 12, 2020
Peer-review started: December 12, 2020
First decision: January 7, 2021
Revised: January 25, 2021
Accepted: April 26, 2021
Article in press: April 26, 2021
Published online: June 19, 2021

P-Reviewer: Barone MTU
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Li JH

exam and imposes tremendous pressure on the third-year high school students.

The COVID-19 epidemic was first reported in China. The teenagers were restricted at home for a long time and were the first to switch to online education. Although the rises of psychosomatic issues caused by COVID-19, especially in teenagers, have been widely reported [3-5], innovative investigation into this issue remains scarce. In this study, we conducted a large cohort survey in a high school at the end of the COVID-19 epidemic in China. We evaluated the prevalence of PTSD symptoms and their associated factors as well as the effects and attitudes towards online education. We further investigated the impact on the final year high school students relating to the college entrance examination.

MATERIALS AND METHODS

Study population

The first, second and third-year students of a high school in Lanzhou, Gansu province of China were invited to participate in this study. They were requested to complete the survey with their parents. The study was conducted from April 20 to April 30, 2020.

Survey instrument

A detailed questionnaire comprising of 65 questions was designed and divided into five sections. The first four sections were designed for all the students, comprising of 11 demographic, 11 COVID-19, 9 online educations and 22 PTSD related questions. The final section consisted of 11 college entrance examination related questions specific for the final year students. The survey was anonymously conducted *via* WeChat, a Chinese multipurpose messaging, social media and mobile payment app.

The 9 online education related questions were designed to assess effectiveness (3 questions), efficiency (3 questions) and satisfaction (3 questions). Each question was comprised of five options including no, low, average, good and excellent.

In this study, we used Impact of Events Scale-Revised (IES-R) self-questioner to examine the psychological impact[6,7]. Further detail has been documented previously [5]. IES-R questioner was translated into Chinese language. IES-R questioner validity and reliability has been extensively reported[8-10].

Statistical analysis

Descriptive statistical analysis was done to demonstrate the demographic characteristics of the participants. First, a univariate analysis was done to screen statistically significant variables, which were subsequently subjected to multivariate logistic regression analyses. The estimations of the strengths of associations were revealed by the odds ratio with a 95% confidence interval. Descriptive and inferential statistics were calculated using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, United States). All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

RESULTS

In total, 893 students participated in the survey. Ten students declined to continue. Therefore, 883 students were included. Participant demographic characteristics were given in Table 1. There were 33.4% first-year, 23.6% second-year and 43.0% final year students. Most students were from the Han ethnic background (98.1%), and 53.2% were girls and 46.8% were boys. The majority of the students were living with parents (96.3%) in urban areas (85.4%) (Table 1).

The majority of students (683 of 866) reported that their families are fully aware of COVID-19. Overall, students reported that they were affected economically (41.6%), psychologically (22.1%), emotionally (6.8%), socially (6.8%) and physically (6.8%) by the COVID-19 epidemic. In contrast, 14.9% of students reported that they were unaffected. A large percentage (93.0%) reported that they have gone back to their normal routine (Table 2). The outbreak negatively affected 68.3% of student's studies. Although 96.5% of the respondents were willing to returning back to schools, 63.0% of students have concerns regarding the risk of getting COVID-19 once back to school. Knowledge about the signs and symptoms of COVID-19 such as fever, difficulty/shortness of breath, cough, flu-like symptoms, diarrhea, fatigue, sore throat and chills were found to be known by 65.2%, 12.9%, 7.6%, 4.4%, 1.6%, 1.0%, 0.9% and

Table 1 Demographic characteristics

Characteristic	Total	%
Sex		
Male	413	46.8
Female	470	53.2
Class		
Class 1	295	33.4
Class 2	208	23.6
Class 3	380	43.0
Ethnic		
Han	866	98.1
Others	17	1.9
Residence		
Urban	754	85.4
Rural	129	14.6
Children		
Single	441	49.9
Double	388	43.9
Multiple	54	6.1
Father education		
Primary or less	82	9.3
Middle	331	37.5
College	299	33.9
University	157	17.8
Not filled	14	1.6
Mother education		
Primary or less	69	7.8
Middle	310	35.1
College	294	33.3
University	191	21.6
Not filled	19	2.2
Father profession		
Farmer	118	13.4
Teacher, doctor and civil	60	6.8
Private company employees	137	15.5
Self-business	47	5.3
Others	506	57.3
Not filled	15	1.7
Mother profession		
Farmer	108	12.2
Teacher, doctor and civil	69	7.8
Private company employees	149	16.9
Self-business	79	8.9

Others	457	51.8
Not filled	21	2.4
Monthly income in RMB		
< 3000	196	22.2
3001-5000	388	43.9
5001-10000	242	27.4
10000	57	6.5
Live with who		
Parents	850	96.3
Grand parents	23	2.6
Caregivers	10	1.1

0.1% of participants, respectively. When students suspect infection, 51.0% of the participants prefer to inform their teachers, whereas 29.7% would go into self-isolation (Table 2).

In this study, a total of 33.0% students had an IES-R score above 20 (Table 3). PTSD symptoms were significantly higher in rural (P = 0.001) compared to urban students. PTSD symptoms were also significantly more prevalent in students whose parents have lower education and profession levels (Table 3).

Students felt that online education was not (10.8%) or less effective (50.1%) for acquisition of knowledge, enlightening practical as well as communication skills. Students reported that it was not (17.9%) or less (43.9%) effective that students were not able to complete their homework, communicate with teachers and take advantages of the multimedia setup. Over half (64.8%) of the students reported that they were not or less satisfied and had difficulties adapting to the online education system (Supplementary Table 1). Correlation analysis revealed that the class level, residential background and whether they lived with parents were significantly associated with satisfaction and effectiveness of the virtual tutoring system (Supplementary Table 2).

This study showed that IES-R scores were substantially associated with residential background, the education level and profession of parents and family monthly income (Supplementary Table 2). According to univariate analysis, residential background, family monthly income and the professions of mother and father were significantly linked with PTSD symptoms. For multiple logistic regression analysis, only residential background remained as a significant factor relating to PTSD symptoms in children (Supplementary Table 3).

In this study, 380 participants were final year students and thus were eligible to fill in the college entrance examination section of the questionnaire. Twenty-seven participants did not complete all questions and were excluded, resulting in 353 students for final analysis. Among them, 74.2% said that the COVID-19 outbreak negatively affected their preparation for the college entrance exam. The outbreak increased psychological pressure for the college entrance examination preparation in 68.0% of students. Although 54.7% students regarded the online learning system as helpful to their preparation, 97.7% said that school opening would be beneficial for preparing for the college entrance examination. The postponement of the college entrance examination was favored by 90.4% of students. There were concerns regarding the risk of getting COVID-19 during the exam from 61.8% of students. To minimize the risk, 41.6% participants said that they would follow strict personal hygiene during the college entrance examination. A face mask would be worn during the exam by 19.5%, and 17.8% would use the mask on the way to the exam and to home. If a student had COVID-19 symptoms during the exam, then 50.7%, 13.3% and 10.2% would notify the proctor, teacher and parents, respectively (Supplementary Table 4).

DISCUSSION

To minimize the spread of COVID-19, China has implemented strict quarantine measures including school closures, travel bans, lockdowns and within-population quarantine. These measures have majorly impacted the mental health of young

Table 2 Prevalence of post-traumatic stress disorder symptoms among high school students

Features	Total	Positive	%	*P* value
Prevalence	883	291	33.0	
Class				0.61
Class 1	295	98	33.2	
Class 2	208	63	30.3	
Class 3	380	130	34.2	
Residence				*0.001*
Urban	754	230	30.5	
Rural	129	61	47.3	
Father education				*0.05*
Primary or less	82	26	31.7	
Middle	331	129	39.0	
College	299	85	28.4	
University	157	48	30.6	
Not filled	14	3	21.4	
Mother education				*0.024*
Primary or less	69	35	50.7	
Middle	310	103	33.2	
College	294	89	30.3	
University	191	57	29.8	
Not filled	19	7	36.8	
Father profession				*0.009*
Farmer	118	55	46.6	
Teach, doctor and civil servant	60	17	28.3	
Private company employees	137	46	33.6	
Self-business	47	18	38.3	
Others	506	153	30.2	
Not filled	15	2	13.3	
Mother profession				*0.019*
Farmer	108	51	47.2	
Teach, doctor and civil servant	69	18	26.1	
Private company employees	149	53	35.6	
Self-business	79	26	32.9	
Others	457	137	30.0	
Not filled	21	6	28.6	

children and adolescents[3,4]. Here, we first measured the COVID-19 epidemic effects on the mental health of high school students. Further, we identified the potential risk factors linked with PTSD symptom development in this youth cohort. Our results showed that 33.0% of students experienced PTSD signs and symptoms due to the COVID-19 epidemic. The high PTSD symptom incidence rate is likely attributed to several factors, including confinement at home, worrying about their academic progress and future plans as well as fearing the risk of infection [3,4,11-15]. We found that PTSD symptoms were significantly higher in rural students and students whose parents have lower levels of education and professions. This is in line with the fact that COVID-19 has had a substantial effect on the global economy, including an increase in

Table 3 Response related to the effects, knowledge and preparedness for coronavirus disease 2019

Inquiry item	*n*	%
Do you and your family understand the COVID-19 outbreak?	866	98.1
COVID-19 affected you physically	60	6.8
COVID-19 affected you economically	367	41.6
COVID-19 affected you psychologically	195	22.1
COVID-19 affected you emotionally	69	7.8
COVID-19 affected you socially	60	6.8
COVID-19 did not affect you	132	14.9
Did you back to your normal routine after COVID-19 epidemic under control in China?	821	93.0
The COVID-19 outbreak has negatively affected your study?	603	68.3
Do you think the COVID-19 outbreak will have a long-term negative impact on your future studies?	221	25.0
Do you think students should gradually return to school?	848	96.0
Are you fully prepared for returning to school?	852	96.5
Do you think there is a risk of getting COVID-19 back to school?	556	63.0
How will you reduce the risk of getting COVID-19 after school opening?		
Strict personal hygiene	294	33.3
Wear a mask on the way to school and home	129	14.6
Wear a mask at school	268	30.4
Avoid eating in the cafeteria	9	1.0
Reduce exchanges and activities between classmates	47	5.3
Avoid or reduce the use of public transportation	38	4.3
Avoid or reduce access to public places	92	10.4
Do not know	5	0.6
No action required	1	0.1
Symptoms of new corona virus infections?		
Fever	576	65.2
Cough	67	7.6
Chills	1	0.1
Difficulty breathing/shortness of breath	114	12.9
Flu-like symptoms	39	4.4
Diarrhea	14	1.6
Fatigue	9	1.0
Sore throat	8	0.9
None of the above	48	5.4
Do not know	7	0.8
What do you do if you feel the symptoms of COVID-19 at school?		
Confidential	2	0.2
Continue school normally	2	0.2
Self-isolation	262	29.7
Take medicine by self-	1	0.1
Visit doctor by self	71	8.0
Notify the teacher	450	51.0

Notify parents	86	9.7
Tell class fellow	1	0.1
Do not know	1	0.1
Others	7	0.8

COVID-19: Coronavirus disease 2019.

the unemployment rate[16]. Families with low social economic status having such economic loss will likely experience immediate effects on their daily livelihood. This will subsequently increase psychological and economic pressure on their children[17].

To minimize education losses, the authorities have swiftly launched online portals and web-based applications and switched the education system to a virtual education system. However, virtual education systems need an efficient and well-organized learning environment and implementation. However, the sudden outbreak of COVID-19 in China caused a substantial variance in virtual systems among schools of different provinces. In this study, the majority of students were not satisfied with online education. The class level of the students, residential background and living with parents were significantly linked with the online education system effectiveness. There are two possible reasons. First, students from higher classes are skilled enough to adapt the virtual education system. Provinces or families with an advanced socioeconomic background are more equipped with the latest technologies. Second, the majority of the participants were not happy with the virtual teaching system. The education department officials should take this issue seriously to improve the virtual education system effectiveness and ensure all students have access to the digital devices and its use.

The final year high school students are facing with mounting pressure of the national college entrance exam. The results of this exam often have a lifelong effect on most Chinese citizens[18]. The college entrance examination usually takes place from June 7 to June 8 every year. The Chinese Ministry of Education postponed the exam by 1 mo due to the COVID-19 epidemic. In our survey, over half of the final year students felt that the COVID-19 outbreak negatively affected their preparation for the exam and increased their psychological pressure. Although half of the students thought the online learning system helped their preparation, almost all the students preferred school opening for better preparation of the college entrance examination. Over 90.0% of students favored the postponement of the college entrance examination. Over half have concerns of the potential risk of getting COVID-19 during the exam, but they are prepared to take precaution measures.

A limitation in this study is that this survey was conducted in a single school in China in a region with a low number of confirmed COVID-19 cases. Therefore, the findings in this study may not represent other schools and regions in China. Finally, we did not study the content of online education in detail in our cohort as it cannot represent the format of other regions because it varies markedly among different schools and regions in China.

CONCLUSION

In this study, we found that 33.0% of high school students have experienced PTSD symptoms due to the COVID-19 epidemic. These symptoms are significantly more common in students living in rural areas and whose parents have a low education level and low grade jobs. The epidemic has affected the preparation of the national college entrance exam for the final year students, but they appreciate the postponement of the exam by 1 mo. Notably, a large proportion of respondents were not satisfied with online education. Therefore, it is suggested that the authorities optimize the online education program and ensure equal opportunities for the students to get access to the digital learning. Our results call for urgent attention from both government and schools to implement effective interventions to manage the psychological effects and the disturbance of education by COVID-19 on children.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) pandemic control measures are disturbing every aspect of our daily lives. School closures have been widely implemented according to COVID-19 cases in the world. Therefore, approximately 90% of the global student population is confined at home.

Research motivation

School education was suddenly replaced with a virtual education system but the education sector was not ready to adopt it. Therefore, the effects of this new education system on student learning remain ambiguous. Additionally, the risks of infection and confinement at home are affecting student education and psychological health.

Research objectives

The current study was designed to explore the prevalence of post-traumatic stress disorder (PTSD) symptoms and their associated factors in high school students and their assessment of the online education system.

Research methods

The first, second and third-year students of a high school at Lanzhou were invited to participate *via* WeChat, a local social media app in this study. Descriptive and inferential statistics were calculated using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, United States). All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

Research results

In total, 883 students were included in this study. Among them, 33.4% were first year, 23.6% were second year, and 43.0% were third year students. The majority (98.1%) of students' families were well-aware of COVID-19. Overall, 41.6% of students were affected economically, and 22.1% were affected psychologically due to the COVID-19 epidemic. Interestingly, 14.9% of students said that they were not affected by the COVID-19 epidemic. In this study, the prevalence of PTSD symptoms was 33.0%, and its prevalence was significantly higher in rural students (P = 0.001) than in urban students. The high prevalence of PTSD symptoms significantly correlated with the education level, residential background, parent's profession and family monthly income.

Research conclusions

In summary, our results showed that the prevalence of PTSD symptoms was 33.0% among high school students due to the COVID-19 epidemic, and a significantly high prevalence occurred in students who live in rural areas and whose parents had low-grade jobs and education level. Our results further highlighted that the COVID-19 epidemic has also affected the final year student's national college entrance exam preparation. Most notably, the majority of respondents were not pleased with the virtual education system.

Research perspectives

Education department officials should take measures to optimize the online education system and guarantee equal access to the digital learning devices. Further, we suggest that effective measures should also be implemented to minimize the risk of psychological issues caused by COVID-19 on students.

ACKNOWLEDGEMENTS

We sincerely thank all the participants who took part in this study.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 June 19; 11(6): 242-252

DOI: 10.5498/wjp.v11.i6.242

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Psychological predictors of bipolarity in panic disorder

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Author contributions: Jeon HJ conceptualized this study; Jeon HJ, Park DH, Ryu SH and Ha JH collected and interpreted the data; Oh DH conducted statistical analysis and wrote the original draft; Jeon HJ revised the manuscript; all authors reviewed and approved the final article.

Institutional review board statement: This study was approved by the Institutional Review Board of Konkuk University Hospital (IRB number: KUMC 2021-01-028).

Informed consent statement: Written informed consent was waived due to the retrospective nature of the study.

Conflict-of-interest statement: The authors have no conflict of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative

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Abstract

BACKGROUND

Panic disorders frequently occur with affective disorders, particularly bipolar disorder. Patients with panic disorder and bipolar disorder are more likely to present with severe symptoms, such as high rates of suicidal behavior, poor symptomatic and functional recovery, and poor drug responses.

AIM

To investigate the psychological characteristics of panic disorder patients related to bipolarity.

METHODS

A total of 254 patients (136 men and 118 women, mean age = 33.48 ± 3.2 years) who were diagnosed with panic disorder were included in the study. Panic disorder with bipolarity (BP+) was defined as a score of ≥ 7 on the Korean version of the Mood Disorder Questionnaire (K-MDQ), and a score lower than 7 was considered as a panic disorder without bipolarity (BP-). Self-report questionnaires were analyzed to examine their association with bipolarity. Psychological tests used in the study were the Mood Disorder Questionnaire (MDQ), Panic Disorder Severity Scale, Beck Depression Inventory, State-Trait Anxiety Inventory (STAI), Temperament and Character Inventory (TCI), and Minnesota Multiphasic Personality Inventory (MMPI). Statistical analyses were performed to evaluate the correlation between bipolarity of panic disorder patients and various psychological test results indicative of psychological characteristics.

RESULTS

Patients with a K-MDQ score of 7 or more were considered to have a history of manic or hypomanic episodes (BP+ group, n = 128), while patients with K-MDQ scores below 7 were defined as those without bipolarity (BP- group, n = 126). The BP+ group were more likely to be unmarried (single 56.2% *vs* 44.4%, P = 0.008)

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: South Korea

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 24, 2021
Peer-review started: February 24, 2021
First decision: April 21, 2021
Revised: May 6, 2021
Accepted: May 24, 2021
Article in press: May 24, 2021
Published online: June 19, 2021

P-Reviewer: Chen TL, Pivac N
S-Editor: Gao CC
L-Editor: A
P-Editor: Xing YX

and younger (30.78 ± 0.59 *vs* 37.11 ± 3.21, $P < 0.001$). Additionally, the BP+ group had significantly higher scores on psychological assessment scales, such as the hypochondriasis, psychopathic deviate, masculinity-femininity, psychasthenia, schizophrenia, and hypomania (Ma) in MMPI, and novelty seeking, harm avoidance and self-transcendence in TCI, and STAI (state and trait) compared to the BP- group. In logistic regression analysis, depression in MMPI, self-directedness in TCI, and age were negatively associated with MDQ score, meanwhile, Ma in MMPI and STAI (trait) were positively associated with MDQ score.

CONCLUSION
The result of this study suggests that almost 50% of patients with panic disorder are likely to have hypomanic or manic symptoms, and certain psychological factors are associated bipolarity in panic disorder.

Key Words: Panic disorder; Bipolar disorder; Bipolarity; Anxiety; Minnesota Multiphasic Personality Inventory; Temperament and Character Inventory

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Core Tip: The close relationship between panic disorder and bipolar disorder has been suggested in the literature. In this study, we showed that panic disorder patients with high anxiety trait were more likely to have bipolar symptoms. Moreover, low self-directedness scores on the Temperament and Character Inventory and high scores on the hypomanic clinical scale in Minnesota Multiphasic Personality Inventory were also associated with bipolarity in patients with panic disorder. We suggest that certain psychological characteristics may help clinician to make a tailored treatment strategy for panic disorder.

Citation: Oh DH, Park DH, Ryu SH, Ha JH, Jeon HJ. Psychological predictors of bipolarity in panic disorder. *World J Psychiatr* 2021; 11(6): 242-252
URL: https://www.wjgnet.com/2220-3206/full/v11/i6/242.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i6.242

INTRODUCTION

Previous studies have shown that patients with bipolar disorder have a high risk of comorbid panic disorder[1]. In addition, patients with bipolar disorder have a higher risk of intra-episode panic disorder during mania[2]. A family study of bipolar disorder showed that there is a possible complex genetic etiology in bipolar disorder and panic disorder comorbidity[1]. MacKinnon *et al*[3] studied 528 members of 57 families for a genetic linkage study of bipolar disorder. They found that 10 families had a higher rate of comorbid panic disorder, suggesting that comorbid panic disorder can be a specific marker for a familial subtype of bipolar disorder. Contreras *et al*[4] found that the anxiety trait is a heritable phenotype in subjects with bipolar I disorder in a study of 619 individuals. In another study, relatives of patients with bipolar disorder and panic disorder comorbidity showed a higher risk of both bipolar disorder and panic disorder[5]. Many studies have found that panic symptoms are prodromal symptoms of bipolar disorder or atypical presentation of bipolar disorder[6,7]. In addition, Wu *et al*[8] compared neuropsychological test scores among a group of bipolar patients with comorbid anxiety disorder, a group of bipolar patients without comorbidity, and a healthy control group. They concluded that patients with bipolar II disorder and comorbid anxiety disorder had the greatest cognitive impairment among the three groups[8]. Moreover, the presence of anxiety disorder in youth increases the risk of bipolar disorder in the future[9].

The lifetime prevalence of panic disorder is approximately 21% of bipolar disorder, which is much higher than approximately 10% of major depressive disorder. Birmaher *et al*[10] found that panic disorder or bipolar disorder are likely to co-occur with other psychological disorders in youths. Moreover, patients with concomitant panic disorder

and bipolar disorder have a higher risk of psychotic symptoms and suicidal ideation. In other studies, patients with panic disorder and comorbid bipolar disorder had higher rates of suicidal behaviors, severe and longer depressive episodes, higher severity of illness scores, poorer treatment outcomes, and lower quality of life[11-14]. In addition, they tend to have a higher risk of rapid switching and a shorter euthymic period[15,16]. Patients with bipolar disorder with high global anxiety levels developed a greater proportion of weeks in major depressive episodes[17]. Therefore, an early diagnosis of bipolarity in panic disorder patients is important to establish an appropriate treatment plan to improve the prognosis of patients.

Antidepressants are often used in the treatment of panic disorder, and it is well known that antidepressant-induced manic symptoms are quite common in such patients[11]. The lack of information regarding bipolar disorder comorbidity in patients with panic disorder can negatively impact the choice of treatment and management, which is the reason why an early diagnosis of bipolar disorder in patients with panic disorder is important in the treatment outcome of patients[7,11]. Previous studies have discussed the prognosis of bipolar disorder according to the presence of panic disorder[8,10-17], however, few studies have investigated bipolarity in patients with panic disorder[18,19]. The aim of this study was to compare clinical characteristics of panic disorder according to the bipolarity, and to investigate factors that predict the potential risk of bipolar disorder in patients with panic disorder.

MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted in Konkuk University Hospital, Korea. A total of 254 consecutive patients, who were newly diagnosed with panic disorder according to the DSM-V (Diagnostic and Statistical Manual of Mental Disorders), were included in the study. The exclusion criteria include history of (1) Schizophrenia like psychosis; (2) Cognitive impairment due to dementia; (3) Intellectual disability; (4) A history of major neurological disorder; (5) Organic mental disorder; and (6) Substance use problem. This study was approved by the Institutional Review Board of Konkuk University Hospital (IRB number: KUMC 2021-01-028), and written informed consent was waived due to the retrospective nature of the study.

Instruments

Demographic data and psychological test results were also collected. Psychological tests included the Mood Disorder Questionnaire (MDQ), Panic Disorder Severity Scale (PDSS), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Temperament and Character Inventory (TCI), and Minnesota Multiphasic Personality Inventory (MMPI).

MDQ, which was used as a screening tool for bipolar disorder, is a self-report instrument that takes approximately five minutes to complete. Patients with scores above the threshold score of 7 were considered as patients with bipolarity (BP+ group) and the remaining were considered as patients without bipolarity (BP- group). The Korean version of the MDQ (K-MDQ) was used in this study, and the validity and reliability of the questionnaire have been proven to be useful for screening bipolar disorder[20].

PDSS is a standard measurement scale for panic disorders. The instrument included seven items associated with symptoms accompanied by panic disorder[21,22]. This study used the Korean version of the PDSS, which has good test-retest reliability and inter-rater reliability[21].

The BDI-II is a self-report checklist for assessing the severity of depressive symptoms. The 21 items included emotional, physiological, and cognitive symptoms of depression. This study used the Korean version of the BDI-II, which is considered a valid and reliable tool[23].

The STAI is a 40-item self-report instrument used to evaluate anxiety symptoms. The State Anxiety Scale measures an individual's current state of anxiety, and the Trait Anxiety Scale evaluates an individual's stable tendency toward anxiety[24]. This study adopted the Korean version of the scale translated by Lee *et al*[21], which has demonstrated fine psychometric properties[24].

The TCI is a self-report questionnaire based on a biosocial personality model. Cloninger's biosocial model of personality was used to develop the TCI questionnaire. The temperament, which is related to the biosocial model of personality, is composed of novelty seeking, harm avoidance, reward dependence, and persistence. The

character is evaluated in three different aspects of a person's characteristics: self-directedness, cooperativeness, and self-transcendence[25]. The Korean version of the TCI was used in the study. The Korean version of the TCI has been reported to be reliable for assessing personality[26].

The MMPI is commonly used in personality and psychopathology assessments of patients[27]. It contains 10 clinical subscale to evaluate personality and psychopathology of patients: hypochondriasis (Hs), depression (D), hysteria (Hy), psychopathic deviate (Pd), masculinity-femininity (Mf), paranoia (Pa), psychasthenia (Pt), schizophrenia (Sc), hypomania (Ma), and social introversion (Si). The Korean version of the MMPI-II was used in this study and has been reported to be reliable in assessing personality and psychological symptoms in Korean adults[28].

Statistical analysis

Kolmogorov-Smirnov test determined whether the data were normally distributed. The Mann-Whitney and chi-square test was conducted to compare demographic and clinical variables between the group with an MDQ score of less than 7 and the group with an MDQ score of 7 or more (BP+ group). The relationships between the MDQ scores and other psychological variables were analyzed using the Spearman's rank correlation analysis and the logistic regression analysis. The statistical significance level was set at $P < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 17.0) software (SPSS Inc., Chicago, IL, United States).

RESULTS

Table 1 presents the characteristics of the participants. The average age at diagnosis was 33.5 years (range, 18-68 years). There were more female (54.7%) than male participants, and most had at least a high school education. The mean score of K-MDQ was 6.4 ± 3.6 (range, 0-13). Half of the patients (n = 128) had high K-MDQ scores (≥ 7). The mean score of K-MDQ was 9.4 ± 1.7 in the BP+ group *vs* 3.4 ± 2.2 in the BP- group.

Patients in the BP+ group were younger (30.78 ± 0.59 *vs* 37.11 ± 3.21) at the time of the diagnosis and were either unmarried or divorced (single 56.2% *vs* 44.4%, $P = 0.008$) compared to patients in the BP-group. (Table 1) However, a gender, a past psychiatric history, and a family history of psychiatric disorders did not significantly differ between the two groups (Table 1). The BP+ group had significantly higher scores on the MMPI clinical scales. These clinical scales include hypochondriasis, psychopathic deviate, masculinity-femininity, psychasthenia, schizophrenia, and hypomania. In addition, BP+ group had significantly different scores in some TCI dimensions than BP- group. Compared to BP- group, BP + group had higher novelty seeking, harm avoidance, and self-transcendence scores, and lower self-directedness and cooperativeness scores. Moreover, the BP+ group also showed higher levels of depressive symptoms as measured by the BDI (31.5 *vs* 21, $P < 0.001$), and anxiety symptoms measured by STAI (state) and STAI (trait) (state: 63 *vs* 57, $P < 0.001$/trait: 61.5 *vs* 51.5, $P < 0.001$) (Table 2).

In correlation analyses (Table 3 and Supplementary Table 1), K-MDQ scores were associated with increasing Hs, D, Pd, Mf, Pa, Pt, Sc, Ma and Si in MMPI clinical scales, TCI novelty seeking, harm avoidance and self-transcendence dimensions, and higher BDI, STAI (state), and STAI (trait) scores. K-MDQ scores were negatively associated with TCI self-directedness dimension scores ($P < 0.05$).

This study used logistic regression analysis to assess the association of K-MDQ and clinical variables, and the age at onset, MMPI (depression), MMPI (hypomanic), TCI (self-directedness), and STAI (trait) were found to be significantly associated with bipolarity in patients with panic disorder (Table 4). Younger age was significantly associated with an increased K-MDQ score (BP+ group). Moreover, in the MMPI and TCI questionnaire, as the MMPI (depression) and TCI (self-directedness) clinical scales decreased, K-MDQ scores increased. In addition, the increase in MMPI (hypomanic) clinical scale scores was significantly associated with the BP+ group (bipolarity of patients). The patients who showed an innate trait of anxiety tested by STAI (trait) tended to be more related to high K-MDQ scores (BP+ group).

Table 1 Comparison of demographic and clinical features between panic disorder with bipolarity and panic disorder without bipolarity groups

	BP+	BP-	*P* value
Demographic features			
Patients: *n* (%)	128 (50.4)	126 (49.6)	
Marital status			0.008
Married: *n* (%)	32 (25.0)	53 (42.0)	
Single: *n* (%)	72 (56.2)	56 (44.4)	
Not answered: *n* (%)	24 (18.7)	17 (13.4)	
Age (yr)	30.78 ± 0.59	37.11 ± 3.21	< 0.001
Gender (M/F, %)	73/55 (57)	63/63 (50)	0.261
Illness history			
Psychiatric history: *n* (%)	41 (32)	32 (25.4)	0.172
Family history: *n* (%)	18 (23.1)	22 (17.5)	0.960

Sex and employment status is expressed as *n* (number of patients, %). Other variables are expressed as mean ± SD. M: Meal; F: Female; BP+: Panic disorder with bipolarity; BP-: Panic disorder without bipolarity.

DISCUSSION

Among the 254 subjects who were diagnosed with panic disorder, approximately 50% of the patients scored 7 or more on the K-MDQ, suggesting a history of manic/hypomanic symptoms in the past. Younger age and the Ma subscale of the MMPI were associated with the higher risk of bipolarity. In addition, the STAI (trait) score, which indicates the innate anxiety level, is positively related to the bipolarity of panic patients, while the self-directedness score in the TCI was negatively associated.

In line with our data, in a previous study, an early age at onset of panic disorder was associated with an increased morbidity risk for bipolar comorbidity[29]. In addition, an early onset of bipolar spectrum disorders is characterized as a severe form of bipolar disorder and tends to have a higher risk of having first-degree relatives with affective disorders[29]. In this study, the patients with bipolarity showed a younger age at onset, which has been found in previous studies[18,30]. Moreover, a previous study has already shown that the risk of anxiety disorder increases as the onset age of bipolar disorder decreases[31]. So, it would be important to evaluate bipolarity thoroughly in younger panic disorder patients in clinics. In our study, patients with a bipolar tendency were more likely to be unmarried at the time of assessment. In previous investigations, bipolar patients had a higher risk of experiencing difficulties in marriages, which is also shown in this study[18,32].

Several psychometric tests have been developed to help diagnose psychiatric patients and the MMPI is one of the most commonly used standardized psychometric tests of adult personality and psychopathology[33]. It is well known that the MMPI Ma subscale is used to identify manic symptoms of individuals at the time of evaluation [34]. In our study, it was found that MMPI hypomanic subscale scores were positively correlated with bipolarity in patients with panic disorder. The result of this study was consistent with previous studies, stating that the high score of hypomanic subscale is indicative of diagnosis of bipolar disorder[35,36]. Higher Ma score in MMPI indicates that patients with panic disorder and bipolarity experience more physical and psychological vitality; however, they also experience dissatisfaction, tension, and anxiety in life[36]. In addition, patients with panic disorder and bipolarity felt less depressed compared to patients without bipolarity, which results from the nature of bipolar disorder manic symptoms.

Engström *et al*[37] conducted a study with 100 euthymic bipolar patients and 100 controls from the normal population to determine the differences in temperament and character of each group. They showed that bipolar patients scored higher in harm avoidance and lower in reward dependence, self-directedness, and cooperativeness in TCI than controls[37]. In addition, in a previous study focusing on the relationship between temperament and panic disorder, high scores of harm avoidance, and reward dependence were related to panic symptoms[38]. The results of our study were

Table 2 Comparison of psychological test result between panic disorder with bipolarity and panic disorder without bipolarity groups

	BP+	BP-	Δ	*P* value
MMPI				
Hs	62 (54, 69)	58 (51, 67.5)	4	0.047[a]
D	67 (57, 77)	66 (54.75, 75)	1	0.149
Hy	60 (53.25, 66)	59 (53, 66)	1	0.391
Pd	61 (48, 67)	51 (44, 59)	10	< 0.001[b]
Mf	52.5 (44.5, 60)	48.5 (39, 57)	4	0.029[a]
Pa	58 (51, 71)	51 (46.5, 62)	7	< 0.001[b]
Pt	65 (55, 76)	59 (49.5, 69)	6	0.001[b]
Sc	62 (50, 74)	51 (44, 61)	11	< 0.001[b]
Ma	53 (45.5, 60)	45 (40, 53)	8	< 0.001[b]
Si	62 (51.5, 70)	59 (47, 67)	3	0.057
TCI				
Novelty seeking	83 (47, 93.75)	47 (20.5, 74)	36	< 0.001[b]
Harm avoidance	94 (76, 99)	89.5 (53.5, 99)	4.5	0.014[a]
Reward dependence	38 (9, 70.75)	33.5 (10, 74)	4.5	0.711
Persistence	20 (6, 62)	18.5 (4, 59.75)	1.5	0.769
Self-directedness	6.5 (1, 22)	28 (4, 62)	21.5	< 0.001[b]
Cooperativeness	22 (3, 52)	34 (13, 52.5)	12	0.022[a]
Self-transcendence	38 (12.5, 67.25)	22.5 (5, 56)	15.5	0.001[b]
BDI	31.5 (20.25, 41)	21 (11.75, 31)	10.5	< 0.001[b]
STAI/state	63 (55.25, 70.75)	57 (44.75, 65.25)	6	< 0.001[b]
STAI/trait	60.5 (53, 67)	51.5 (41.75, 59)	9	< 0.001[b]
PDSS	13.5 (10, 19)	12.5 (8, 17)	1	0.082

[a]$P < 0.05$.

[b]$P < 0.01$. BP+: Panic disorder with bipolarity; BP-: Panic disorder without bipolarity; BDI: Beck Depression Inventory; MMPI: Minnesota Multiphasic Personality Inventory; TCI: Temperament and Character Inventory; STAI: State-Trait Anxiety Inventory; PDSS: Panic Disorder Severity Scale; Hs: Hypochondriasis; D: Depression; Hy: Hysteria; Pd: Psychopathic deviate; Mf: Masculinity-feminity; Pa: Paranoia; Pt: Psychasthenia; Sc: Schizophrenia; Ma: Hypomania; Si: Social introversion.

consistent with those of a previous study indicating that patients with bipolarity showed a negative relationship with self-directedness scores in the TCI test. This result suggests that panic disorder patients with bipolarity are more likely to be aimless and inept than panic disorder patients without bipolarity. The TCI harm avoidance, reward dependence, and cooperativeness scores did show some correlation with bipolarity based on our correlation analyses, but not in our regression analysis. This suggests that a lower self-directedness score can be used as a marker to predict bipolarity in patients with panic.

In this study, the STAI (trait) score was positively related to the bipolarity of patients with panic disorder. High levels of anxiety were positively correlated with bipolarity, particularly when having anxious characteristics in patients with panic disorder. Bipolarity was more related to the anxious characteristics of patients than to the current anxiety levels. In other words, patients with higher anxiety levels and anxiety sensitivity were more likely to be diagnosed with bipolar disorder in the future. Anxiety sensitivity is known to be a contributing factor to the high prevalence and severity of panic disorder comorbid with bipolar disorder, particularly during the manic state of bipolar disorder, as our study has suggested[19]. Contreras *et al*[39] found a significant positive correlation between trait anxiety score and mania episodes in lifetime. However, there was no correlation between trait anxiety scores and lifetime depressive episodes. Azorin *et al*[40] also stated that an irritable temperament is a

Table 3 Correlation analyses between Korean version of the Mood Disorder Questionnaire score and other measured variables

	R	*P* value
Age	-0.298	< 0.001[b]
MMPI		
Hs	0.144	0.022[a]
D	0.146	0.020[a]
Pd	0.340	< 0.001[b]
Mf	0.147	0.019[a]
Pa	0.389	< 0.001[b]
Pt	0.294	< 0.001[b]
Sc	0.405	< 0.001[b]
Ma	0.455	< 0.001[b]
Si	0.161	0.010[b]
TCI		
Novelty seeking	0.426	< 0.001[b]
Harm avoidance	0.218	< 0.001[b]
Reward dependence	0.017	0.788
Persistence	0.020	0.753
Self-directedness	-0.353	< 0.001[b]
Cooperativeness	-0.163	0.009[b]
Self-transcendence	0.286	< 0.001[b]
BDI	0.404	< 0.001[b]
STAI/state	0.314	< 0.001[b]
STAI/trait	0.468	< 0.001[b]
PDSS	0.171	0.006[b]

[a]$P < 0.05$.

[b]$P < 0.01$. BP+: Panic disorder with bipolarity; BP: Panic disorder without bipolarity; BDI: Beck Depression Inventory; MMPI: Minnesota Multiphasic Personality Inventory; TCI: Temperament and Character Inventory; STAI: State-Trait Anxiety Inventory; PDSS: Panic Disorder Severity Scale; Hs: Hypochondriasis; D: Depression; Hy: Hysteria; Pd: Psychopathic deviate; Mf: Masculinity-feminity; Pa: Paranoia; Pt: Psychasthenia; Sc: Schizophrenia; Ma: Hypomania; Si: Social introversion.

source of mood instability and stress, which interacts with other temperamental characteristics to induce both anxiety and bipolar symptoms. In addition, studies have shown that when the level of anxiety sensitivity is high, the prognosis of patients with bipolar disorder is worse and panic disorder symptoms are more severe[7,19,41,42]. Therefore, it is important to make an evaluation about panic disorder patients' anxiety sensitivity to diagnose bipolar disorder for a better prognosis.

This study has several limitations. First, this study was a cross-sectional, retrospective study with relatively small number of participants. We included consecutive patient who were clinically diagnosed with panic disorder based on the strict diagnostic criteria. However, the study design may be related to the selection bias and hinder the generalizability of the results. Second, even though we have consulted a biomedical statistician to confirm the proper statistical method to use in the study, there is a possibility of type I error because the *P* value was not corrected in the multiple comparison. Finally, a self-report questionnaire was used to evaluate the bipolarity. The MDQ is a validated questionnaire for evaluating manic/hypomanic symptoms in patients with various psychiatric conditions, however, clinicians did not confirm the history of manic/hypomanic symptoms of the participants in this study.

Table 4 Logistic regression analysis showing the association of panic disorder with bipolarity group (Korean version of the Mood Disorder Questionnaire score ≥ 7) with clinical variables

	Odds ratio	*P* value	95%CI
Age	0.973	0.042[a]	0.947-0.999
MMPI/D	0.963	0.027[a]	0.932-0.996
MMPI/Ma	1.080	0.000[b]	1.040-1.122
TCI/self directedness	0.980	0.013[a]	0.965-0.996
STAI/trait	1.062	0.006[b]	1.017-1.108

[a]$P < 0.05$.

[b]$P < 0.01$. MMPI: Minnesota Multiphasic Personality Inventory; TCI: Temperament and Character Inventory; STAI: State-Trait Anxiety Inventory; D: Depression; Ma: Hypomania; CI: Confidence interval.

CONCLUSION

In this study, we were able to predict bipolarity in panic disorder patients through simple self-report questionnaires, which have been widely used. Early diagnosis of bipolarity in patients with panic disorder will have a positive effect on the patient's treatment outcome. It should be noted that among patients with panic disorder, patients with an anxious personality have a high comorbidity rate for bipolar disorder. Based on the results of this study, it is possible to detect bipolarity in advance through a simple questionnaire in actual clinical practice.

ARTICLE HIGHLIGHTS

Research background

Panic disorders frequently occur with affective disorders, particularly bipolar disorder. The lifetime prevalence of panic disorder is about 21% of bipolar disorder, much higher than about 10% of major depressive disorder. Patients with panic disorder and bipolar disorder are more likely to present with a severe course of disorder, such as high rates of suicidal behavior, poor symptomatic and functional recovery, and poor drug responses.

Research motivation

Patients who suffer from both panic disorder and bipolar disorder have a poorer prognosis than patients who suffer from only one disorder. So, it is crucial to predict a bipolarity of a patient who is diagnosed with panic disorder at early phase of disease course to select a proper treatment for the patients. However, there is no standard evaluation tool to predict a bipolarity of panic disorder patients.

Research objectives

In this study, we tried to identify the specific symptoms of patients with panic disorder that indicate bipolarity to establish a proper treatment plan.

Research methods

A total of 254 patients (136 men and 118 women, mean age = 33.48 ± 3.2 years) were diagnosed with panic disorder. Panic disorder with bipolarity (BP+) was defined as a score of ≥ 7 on the Korean version of the Mood Disorder Questionnaire (K-MDQ), and a score lower than 7 was considered a panic disorder without bipolarity (BP-). Self-report questionnaires were analyzed to examine their association with bipolarity. Psychological tests included the Mood Disorder Questionnaire (MDQ), Panic Disorder Severity Scale, Beck Depression Inventory, State-Trait Anxiety Inventory (STAI), Temperament and Character Inventory (TCI), and Minnesota Multiphasic Personality Inventory (MMPI). Statistical analyses were performed to evaluate the correlation between panic disorder and bipolarity. Our collected data was not normally distributed. So, for statistical analysis, we used Mann-Whitney test to compare continuous variables between two groups, and Spearman's rank correlation to find the relationship between the MDQ scores and other variables.

Research results

Patients with a K-MDQ score of 7 or more were considered to have a history of manic or hypomanic episodes (BP+ group, n = 128), while patients with K-MDQ scores below 7 were defined as those without bipolarity (BP- group, n = 126). The BP+ group were more likely to be unmarried (single 56.2% *vs* 44.4%, P = 0.008) and younger (30.78 ± 0.59 *vs* 37.11 ± 3.21, P < 0.001). Moreover, the BP+ group had significantly higher scores on some psychological assessment scales, such as the hypochondriasis, psychopathic deviate, masculinity-femininity, psychasthenia, schizophrenia, and hypomania (Ma) in MMPI, and novelty seeking, harm avoidance and self-transcendence in TCI, and STAI (state and trait) compared to the BP- group. In logistic regression analysis, MMPI (depression), MMPI (paranoia), and age were negatively associated; however, MMPI (Ma) and STAI (trait) were positively associated with the BP+ group (K-MDQ score ≥ 7). In addition, BP+ was positively associated with current manic symptoms (1.080, P = 0.000) and trait anxiety (1.062, P = 0.006), and negatively associated with current depressive symptoms.

Research conclusions

The result of this study suggests that MMPI, TCI and STAI can be used to predict the bipolarity of panic disorder patients. These psychological assessments can be considered to performed in clinics to establish proper treatment plans for a better prognosis.

Research perspectives

Further investigations should aim to assess the validity of specific psychological factors to be used to detect bipolarity in panic patients prospectively.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 June 19; 11(6): 253-264

DOI: 10.5498/wjp.v11.i6.253

ISSN 2220-3206 (online)

SCIENTOMETRICS

Current global research landscape on COVID-19 and depressive disorders: Bibliometric and visualization analysis

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Author contributions: Al-Jabi SW developed the concept for the manuscript, reviewed the literature, formulated research questions, collected the data, conducted analyses, and interpreted the data; Al-Jabi SW read and approved the final manuscript.

Conflict-of-interest statement: The author declares that she has no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) has affected daily life globally dramatically over the last year. The impact of the COVID-19 epidemic on mental health is expected to be immense and likely to be long-lasting, raising a range of global problems that need to be addressed accordingly.

AIM

To analyze the Scopus-based depression research and COVID-19, explain the advancement of research nowadays, and comment on the possible hotspots of depression research and COVID-19 to obtain a more global perspective.

METHODS

In this report, bibliometric analysis and visualization are used to explain COVID-19's global research status on depression and provide researchers with a guide to identify future research directions. Relevant studies on depression and COVID-19 were retrieved from the Scopus database. Visualization maps were produced using the VOSviewer software, including research collaboration.

RESULTS

At the time of data collection (November 18, 2020), 77217 documents were released by Scopus to COVID-19 in all areas of research. By limiting the search to depression and COVID-19 (January 2020 up until November 18, 2020), there are 1274 published articles on depression and COVID-19 in the Scopus. The great majority of which are original articles (n = 1049, 82.34%), followed by 118 review articles (9.26%), 66 letters (5.18%). The United States had the highest number of publications at 282 (22.14%), followed by China (19.07%) at 243 and Italy at 121 (9.5%). The major two clusters are signified by mental health outcomes among the general population and mental health outcomes among health care workers.

CONCLUSION

The evidence from this study found that many articles focused on mental health

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Palestine

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 13, 2021
Peer-review started: January 15, 2021
First decision: March 30, 2021
Revised: April 2, 2021
Accepted: May 24, 2021
Article in press: May 24, 2021
Published online: June 19, 2021

P-Reviewer: Huang Y
S-Editor: Gao CC
L-Editor: A
P-Editor: Li JH

outcomes among the general population and health care workers. With adequate psychological support offered by the government or community agencies, mental health in various communities should be put within the local and global public health agenda. This changing situation involves the scientific community's collaborative efforts to contribute to population monitoring during quarantine and COVID-19 outbreaks and to examine the short- and long-term adverse effects on psychological well-being.

Key Words: Depression; COVID-19; Bibliometric; Scopus; Psychological distress

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Core Tip: This is the first study to describe and visualize scientific research on coronavirus disease 2019 (COVID-19) and its effect on depression. Therefore, the current study would enable professionals, psychiatrists, and experts from other fields of medicine, in addition to local authorities and community health staff, to obtain an empirical view of the evolution of this topic because current knowledge on the main psychological distress effects of COVID-19 is scarce and little is known in the development of research on this topic.

Citation: Al-Jabi SW. Current global research landscape on COVID-19 and depressive disorders: Bibliometric and visualization analysis. *World J Psychiatr* 2021; 11(6): 253-264
URL: https://www.wjgnet.com/2220-3206/full/v11/i6/253.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i6.253

INTRODUCTION

In December 2019, new cases of pneumonia of unknown causes were detected in Wuhan city. In Jan 2020, Chinese authors identified a novel coronavirus, which was later known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19). After that incidence, COVID-19 was spared in several places in the world, then the World Health Organization considered the SARS-CoV-2 virus as a pandemic disease on March 11, 2020[1]. Like other coronaviruses, COVID-19 is transmitted by respiratory droplets or contact routes. Most people affected by this novel virus experienced mild to moderate symptoms such as dry cough, fever, sputum production, shortness of breathing, headache, chills, sore throat, joint and muscle itches, *etc.* Symptoms become serious and severe in elderly patients and in people who have chronic diseases[2]. As of November 21, 2020, more than 56.9 million COVID-19 cases and more than 1.3 million death cases from the disease have been reported worldwide[3].

A condition of socio-economic crisis and deep psychological trauma rapidly emerged worldwide as a result of the advent of the COVID-19 epidemic[4]. The current COVID-19 pandemic may have psychological implications for many reasons [5]. Some of these reasons, including physical distance, fear of infection, inadequate information, stigma, quarantine measures, contribute to the pandemic, and government response[6]. As a result of such experiences, such as social isolation, widespread anxiety; unemployment, and financial difficulties; and stress in health-care workers, both the infected and noninfected population may be susceptible[5]. These major stressors have anticipated that lead to an elevated risk of psychopathology, such as depression or anxiety[7,8]. A recent meta-analysis study was designed to review community-based depression studies performed during the COVID-19 epidemic and found that depression rates may be seven times higher in the general population in the COVID-19 outbreak[9]. Another United States study found that the prevalence of depressive symptoms among adults during the COVID-19 pandemic was more than three times higher than the most recent population-based mental health estimates in the United States[10]. In China, 50.4% of health care workers who were exposed to COVID-19 patients reported symptoms of depression[11].

Several systematic reviews or meta-analysis studies show the increasing number of publications addressing the effect of COVID-19 on mental health published from

numerous countries during the outbreak[5,8,12-16]. To date, there is not a bibliometric study assessing depression research and COVID-19 at the global level. In several studies in virology[17-22], more specifically on the COVID-19 outbreak[23-29], bibliometric analysis means evaluating the research output of authors, countries, journals, and institutions[30,31]. Capturing the relevant literature is essential and promotes the comprehension of a particular focus area's characteristics and patterns. It can also rapidly and reliably present the most relevant study, which provides the theoretical foundation for further research. Therefore, we performed the bibliometric analysis to analyze the Scopus-based depression research and COVID-19, explain the advancement of research nowadays, and comment on the possible hotspots of depression research and COVID-19 to obtain a more global perspective. Because current knowledge on the key psychological distress impacts of COVID-19 is scarce and little is known in the production of reports on this subject, a descriptive and visual quantification of scientific research on COVID-19 and its impact on depression will allow information professionals, psychiatrists, and experts from other fields of medicine, in addition to local authorities and community health staff, to obtain an empirical view of evolution, current scope, and depression.

MATERIALS AND METHODS

Data source

Scopus is known for bibliometric research as one of the most appropriate online databases. In the Scopus online database, we pick the 'Advanced search" feature and insert keywords to obtain all publications related to COVID-19 and depression literature between January 1, 2020, and November 18, 2020.

Search strategies

To avoid possible bias produced by continuous database update, the retrieval and export of publications should be created within one day (November 18, 2020). The retrieval and export of documents should be done within one day to prevent any bias in data collection that might be caused by constant updating of the database. This research's retrieval method was as follows: Step 1: The terms related to COVID-19 entered into the Scopus engine were chosen from the related studies on COVID-19 to achieve the goals of this study. All following ''terms'' were entered as ''Article Title/Abstract/Keywords'': "COVID 19" OR "coronavirus 2019" OR "2019 novel coronavirus" OR "2019-novel CoV" OR "coronavirus disease 2019" OR "2019 ncov" OR COVID19 OR "COVID 2019" OR "corona virus 2019" nCoV2019 OR "nCoV-2019" OR "nCoV 2019" OR COVID-19 OR 2019-ncov OR "SARS-CoV-2" OR "Severe acute respiratory syndrome coronavirus 2". Step 2: We then restricted our collected publications in step 1 to all those included in their title or/And Abstract depression and related terms. The terms related to depression entered into the Scopus engine were chosen from previous related studies on depression[32,33]. All the following ''terms'' were entered as ''Article Title/Abstract'': depression OR depressive OR "seasonal affective" OR "dysthymia" OR "affective disorder" OR "mood disorder" OR "bipolar disorder". Step 3: We omitted publications that had been indexed as an erratum. No language restriction was imposed on the literature search.

Bibliometric analysis

The following bibliometric parameters were assessed: Publication count, authorship, citation count, institution, country/region, journal, document type, and *h*-index.

Visualise analysis

To evaluate the collaborative relationships between countries/regions, VOSviewer 1.6.15 software was used to construct network visualization maps[34]. In addition, VOSviewer will identify terms with high frequencies of co-occurrence into many clusters and color them simultaneously. The co-occurrence analysis of terms is a significant method to determine the hotspots related to COVID-19 and depression research. By counting the number of times that terms frequently appear in both titles and abstracts of the selected publications, the principle is to determine the value of terms. The minimum number of recurring terms is 20 by setting the counting method to binary counting.

RESULTS

At the time of data collection, 77217 documents were released by Scopus to COVID-19 in all areas of research. By limiting the search to depression and COVID-19 (January 2020 up until November 18, 2020), there are 1274 published articles on depression and COVID-19 in the Scopus. The great majority of which are original articles (n = 1049, 82.34%), followed by 118 review articles (9.26%), 66 letters (5.18%), and 41 (3.22%) were others.

Publications analyzed in this study were authored by researchers from 95 countries. Of the overall publications, the top 10 countries accounted for 88.93% (1133 documents) (Table 1). The United States had the highest number of research outputs at 282 (22.14%), followed by China (19.07%) at 243 and Italy at 121 (9.5%). International research collaboration among active countries was assessed in countries with a minimum contribution of 10 publications (Figure 1). The United States, followed by China and Italy are at the heart of collaboration and have the strongest alliance partnerships in research with other countries.

Table 2 shows the ten institutions that have contributed the most in the field of depression and COVID-19. Among them, the Huazhong University of Science and Technology in China published the most documents (29 publications). This was followed by Tongji Medical College from China (28 publications), the University of Toronto from Canada (23 publications), and Università Degli Studi di Roma La Sapienza from Italy (23 publications).

Table 3 illustrates the top 10 most popular journals for publishing articles linking COVID-19 and depression. The International Journal of Environmental Research and Public Health had the largest number of published articles (61 publications, 4.79% of all documents), followed by Psychiatry Research (48, 3.77%), Journal of Affective Disorders (46, 3.61%), and Frontiers in Psychiatry (33, 2.59%).

The ten most cited publications have been listed in Table 4 along with the total number of citations per document. There were 8206 citations for 569 documents, with 16 documents having a minimum of 100 citations. The h-index was 35, and, on average, each paper earned 6.44 citations. The citation counts for the top 10 most cited articles in the range of 151 to 887[11,15,35-42].

We analyzed all included 1274 publications using the VOSviewer. In Figure 2, among the 22839 terms, only 399 terms (defined as terms that occurred more than 20 times appeared in titles and abstracts in all publications) were divided into 3 clusters. The major two clusters are represented by two colored clusters. Cluster number 1 (red color) contained terms such as “economy”, “isolation”, “home order”, “home”, “physical activity”, “daily life”, “lockdown”, “citizens’ wellbeing”, “child”, or “social distancing” linked to mental health outcomes in the general population. While Cluster number 2 (green color) contained terms such as “health care worker”, “medical staff”, “depression scale”, “insomnia severity index”, “severe depression”, or “depression symptoms” linked to mental health outcomes amongst health care workers.

DISCUSSION

This research is the first bibliometric analysis of depression-related publications following the pandemic of COVID-19. The appropriate bibliometric indicators for analyzing 1274 relevant research works have been followed in this study. Our rapid review of available studies demonstrated that the COVID-19 pandemic had produced a global emergency in less than a couple of months. This infectious virus does not only pose concerns about public health in general but also causes several psychological and behavioral diseases.

High-income countries, including the United States, China, Italy, United Kingdom, and Canada, are the leaders in the world in depression-related publications following the COVID-19 pandemic, which contribute to more than 65% of the total publications. The high prevalence of COVID-19 in those experiencing the first outbreak is a possible explanation for these results[43-49]. Most studies were carried out within populations from highly educated, high-income, and Western nations in particular. These settings can make successful mental health treatment much more imperative and give more attention to non-Western environments, which characterize by the higher population density[50]. There is still limited information available on the COVID-19 pandemic's mental health impact in low- and middle-income countries[51]. The prevalence of depression symptoms in low- and middle-income countries is close to that recorded during the pandemic in most high-income countries[51]. People with low socioeco-

Table 1 List of the top 10 countries with the highest coronavirus disease 2019 studies related to depression between January 1, 2020, and November 18, 2020

Ranking	Country	Number of documents	%
1st	United States	282	22.14
2nd	China	243	19.07
3rd	Italy	121	9.50
4th	United Kingdom	103	8.08
5th	Canada	82	6.44
6th	India	81	6.36
7th	Spain	76	5.97
8th	Australia	56	4.40
9th	Brazil	45	3.53
10th	Germany	44	3.45

Table 2 List of the top 10 institutions with the highest coronavirus disease 2019 studies related to depression between January 1, 2020, and November 18, 2020

Ranking	Institution	Country	*n*	%
1st	Huazhong University of Science and Technology	China	29	2.28
2nd	Tongji Medical College	China	28	2.20
3rd	University of Toronto	Canada	23	1.81
3rd	Università degli Studi di Roma La Sapienza	Italy	23	1.81
5th	Central South University	China	21	1.65
5h	Mental Health Center	China	21	1.65
7th	Harvard Medical School	United States	16	1.26
7th	King's College London	United Kingdom	16	1.26
7th	Fondazione Policlinico Universitario Agostino Gemelli	Italy	16	1.26
10th	National University of Singapore	Singapore	15	1.18
10th	Renmin Hospital of Wuhan University	China	15	1.18

nomic status are also at a higher risk of contracting COVID-19 and its complications, which include death as well as mental health concerns[52,53]. Notably, clinically relevant post-traumatic stress disorder symptoms were identified in about 30% of COVID-19-infected patients who required hospitalization at the early stage of infection or months later[5,54]. Immunological mechanisms and inflammatory biomarkers, fear of disease, anxiety about the future, stigma, traumatic memories of serious illness, and social alienation encountered by patients during the COVID-19 are all important psychological stressors that may interact in determining psychopathological outcome [55,56].

Our study showed that the United States was the most prolific country in research output in the depression-related COVID-19 pandemic, leading to more than 20 percent of the topic's publications. Perhaps this United States research production is because of the large size of the economic power or population. In addition, most of the social networking sites in the United States were developed and built. These results are close to earlier bibliometric studies in various fields[57-61], primarily because the United States has the highest activity in the worldwide development of scientific research and international cooperation networks[62,63].

This study has found that, generally, many articles focused on mental health outcomes among the general population and health care workers. A clear theme to arise from the findings is that the most widely cited depression-related publications following the COVID-19 pandemic illustrated a variety of subtopics as well as hot research topics. The most cited article was by Wang *et al*[41] and published in the

Table 3 List of the top 10 journals with the highest number of coronavirus disease 2019 studies related to depression between January 1, 2020, and November 18, 2020

Ranking	Journal	*n*	%	IF
1st	*International Journal of Environmental Research and Public Health*	61	4.79	2.849
2nd	*Psychiatry Research*	48	3.77	2.118
3rd	*Journal of Affective Disorder*	46	3.61	3.892
4th	*Frontiers in Psychiatry*	33	2.59	2.849
5th	*Frontiers in Psychology*	29	2.28	2.067
6th	*PLoS One*	27	2.12	2.740
7th	*Brain Behavior and Immunity*	20	1.57	6.633
7th	*International Journal of Social Psychiatry*	20	1.57	1.439
9th	*American Journal of Geriatric Psychiatry*	15	1.18	3.393
9th	*Journal of Medical Internet Research*	15	1.18	5.034

Impact factor is the impact factor for 2019 journals listed in Clarivate Analytics, Incites Journal Citation Reports. IF: Impact factor.

Table 4 List of the top 10 cited articles for coronavirus disease 2019 studies related to depression between January 1, 2020, and November 18, 2020

Ranking	Ref.	Source title	Cited by
1st	Wang *et al*[41], 2020	*International Journal of Environmental Research and Public Health*	887
2nd	Lai *et al*[11], 2020	*JAMA network open*	719
3rd	Qiu *et al*[39], 2020	*General Psychiatry*	390
4th	Rajkumar[15], 20200	*Asian Journal of Psychiatry*	264
5th	Wang *et al*[42], 20200	*Brain, Behavior, and Immunity*	213
6th	Ahorsu *et al*[35], 20200	*International Journal of Mental Health and Addiction*	206
7th	Torales *et al*[40], 20200	*International Journal of Social Psychiatry*	200
8th	Huang and Zhao[37], 20200	*Psychiatry Research*	197
9th	Gao *et al*[36], 20200	*PLoS One*	152
10th	Li *et al*[38], 20200	*International Journal of Environmental Research and Public Health*	151

International Journal of Environmental Research and Public Health, which was cited 887 times. This China study demonstrated that over fifty percent of the respondents rated their psychological effects as mild to extreme during the initial phase of the COVID-19 outbreak. A greater psychological effect of the outbreak and higher levels of depression were correlated with female gender, student, and particular physical symptoms. The higher negative psychological impact was associated with longer quarantine periods, fear of infection, insufficient knowledge, stigma, or financial loss. It is expected that these significant stressors will contribute to an increased risk of depression[9].

The second most cited article was by Lai *et al*[11] and published in *JAMA network open*, was cited 719 times. This is also a Chinese study that found that in hospitals with COVID-19 patients, health care staff reacting to the spread of COVID-19 recorded high rates of depression symptoms and distress. Faced with this critical situation; health care staff who are at the front-line and are actively involved in the diagnosis, recovery, and care of COVID-19 patients are at risk of experiencing psychiatric depression and other signs of mental health. The ever-increasing number of COVID-19 cases, disproportionate workload, few personal security services, extensive media attention, lack of specific medications, and feelings of insufficient help can all add to these stressors, which leads to the mental burden of health professionals[11,64-66]. Therefore, mental health issues must also be incorporated into COVID-19 management, including psychiatric symptoms (*e.g.*, depression or anxiety) monitoring, and social requirements

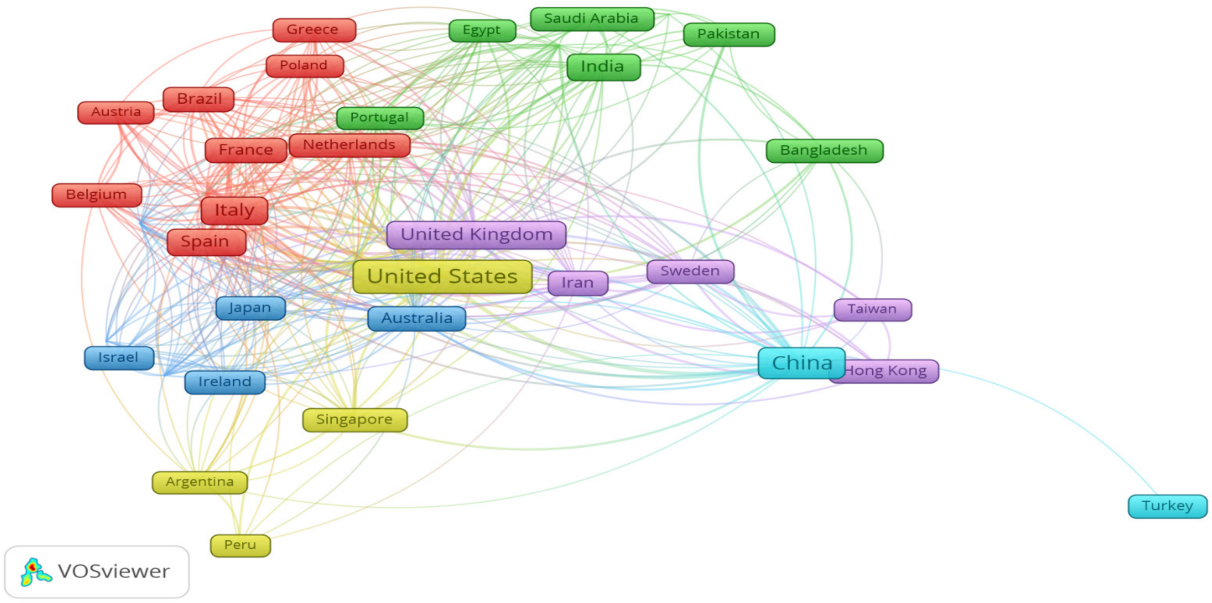


Figure 1 Network visualization map for international collaboration on for publishing articles linking coronavirus disease 2019 and depression.

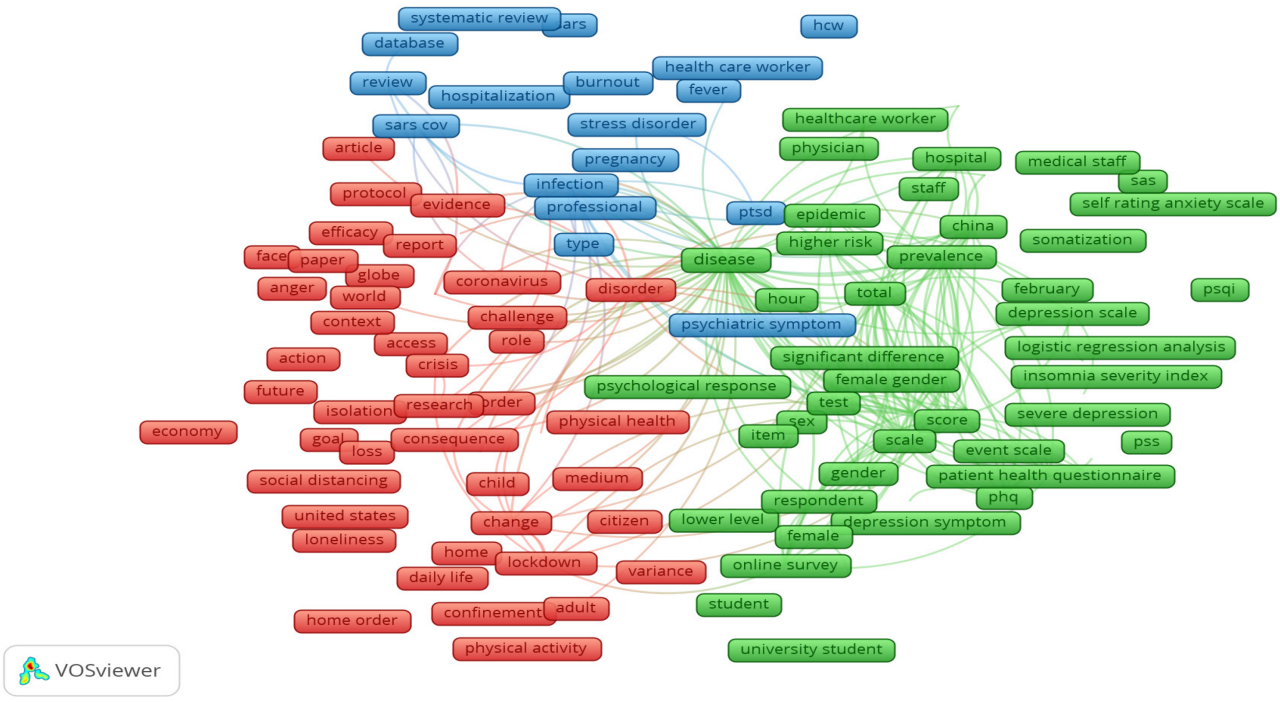


Figure 2 Network visualization map of the most common terms in the retrieved literature's titles/abstracts that refer to coronavirus disease 2019 and depression. The three clusters represent the major research themes in the retrieved literature.

within the general population[8,67].

This bibliometric review represents the first concise overview of global depression-related publications following the COVID-19 pandemic. It illustrates the advantages of bibliometric analysis in a structured manner for assessing research productivity. There were some limitations that we should explain. First, the publications are only derived from Scopus. Second, due to the online database's continuous updating, there is a certain deviation between our bibliometric research outcomes and the actual findings. Regarding this issue, new studies are still being published, and the number of new studies is expected to appear during the upcoming months.

CONCLUSION

During the initial stage of the COVID-19 epidemic, this bibliometric analysis can enable researchers to discover the current status and emerging trends in depression-related publications. High-income countries which include the United States, China, Italy, United Kingdom, and Canada, are the leaders in the world in depression-related publications following the pandemic of COVID-19, contributing to the majority of the total published literature. The United States had the most collaboration with other countries worldwide. The research has also shown that a large number of articles focused on mental health outcomes among the general population and health care workers. With adequate psychological support offered by the government or community agencies, mental health in various communities should be put within the local and global public health agenda. This changing situation involves the scientific community's collaborative efforts to pay attention to population monitoring during quarantine and COVID-19 outbreaks and examine the short- and long-term adverse effects on psychological well-being.

ARTICLE HIGHLIGHTS

Research background

Over the last year, coronavirus disease 2019 (COVID-19) has had a major impact on daily life around the world. The COVID-19 epidemic is predicted to have a massive and long-lasting effect on mental health, resulting in a range of global issues that must be tackled.

Research motivation

To date, there is not a bibliometric study assessing depression research and COVID-19 at the global level. Capturing relevant literature is important for understanding the characteristics and trends of a specific focus area. It can also rapidly and reliably present the most relevant studies regarding depression research and COVID-19, which provides the theoretical foundation for further research.

Research objectives

This bibliometric analysis was conducted to examine Scopus-based depression research and COVID-19, clarify current research progress, and illustrate the potential hotspots in depression research and COVID-19 in order to gain a more global perspective.

Research methods

The Scopus database was used to find relevant research on depression and COVID-19. The VOSviewer program was used to build visualization maps, which included research collaboration.

Research results

During the initial stage of the COVID-19 epidemic, this bibliometric analysis can enable researchers to discover the current status and emerging trends in depression-related publications. High-income countries which include the United States, China, Italy, United Kingdom, and Canada, are the leaders in the world in depression-related publications following the pandemic of COVID-19, contributing to the majority of the total published literature. The United States had the most collaboration with other countries worldwide. The research has also shown that a large number of articles focused on mental health outcomes among the general population and health care workers.

Research conclusions

According to the findings of this report, several articles focused on mental health outcomes in the general population and among health-care staff. Mental health in diverse populations should be included in the local and global public health agenda with sufficient psychological support provided by the government or community organizations.

Research perspectives

Because current knowledge on the key psychological distress impacts of COVID-19 is scarce and little is known in the production of reports on this subject, a descriptive and visual quantification of scientific research on COVID-19 and its impact on depression will allow information professionals, psychiatrists, and experts from other fields of medicine, in addition to local authorities and community health staff, to obtain an empirical view of evolution, current scope, and depression.

ACKNOWLEDGEMENTS

I would like to thank the Clinical Research Centre of An-Najah National University Hospital for the constant support and wise advice.

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7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
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Help Desk: https://www.f6publishing.com/helpdesk
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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 July 19; 11(7): 265-402



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World Journal of Psychiatry

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The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Lin-YuTong Wang*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
July 19, 2021

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https://www.f6publishing.com

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E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 265-270

DOI: 10.5498/wjp.v11.i7.265

ISSN 2220-3206 (online)

EDITORIAL

Cognitive screening for adult psychiatric outpatients: Comparison of the Cognivue® to the Montreal Cognitive Assessment

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Author contributions: Rose AF designed the overall project concept and study design, analyzed data, and outlined the manuscript; Gilbertson AF contributed to the content of the research study, interpretation of data, and manuscript; Cottrell C contributed to study design, review of literature, and revising manuscript; Tampi RR contributed to study design and revising manuscript.

Conflict-of-interest statement: There is no conflict of interest.

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Abstract

In this editorial we comment on the article by Cahn-Hidalgo D published in a recent issue of the *World Journal of Psychiatry* 2020; 10(1); 1-11. We focus on the importance of utilizing psychometrically valid cognitive screening tools when assessing for cognitive decline in older adults in a psychiatric outpatient setting. We compared the use of Cognivue® to use of the montreal cognitive assessment (MoCA) as a cognitive screening tool. A total of 58 patients aged 55 and over participated in this comparison study. Patients completed cognitive screening on Cognivue®, a new Food and Drug Administration-cleared computer screening device, and the MoCA. The results of patient performance using these two instruments were analyzed. Sixteen (28%) patients screened negative for cognitive impairment on both assessments. Forty-two (72%) patients screened positive on one or both of the assessments. There was 43% agreement between Cognivue® and the MoCA in identifying patients with cognitive impairment, and individual subtests were weakly correlated. The MoCA was determined to be the preferred instrument due to its high sensitivity and specificity (100% and 87%, respectively) when screening for cognitive impairment. We propose that the use of Cognivue® cognitive screening tool be closely reviewed until more research proves that the test meets the standards for reliability and validity. It is important for clinicians to remember that screeners should not be used to diagnosis patients with neurocognitive disorders; instead, they should be used to determine whether further evaluation is warranted. Additionally, misdiagnosing of neurocognitive disorders can pose unnecessary psychological and emotional harm to patients and their families and also lead to incorrect treatment and undue healthcare costs.

Key Words: Dementia; Cognitive screening test; Cognitive impairment; Psychological assessment; Neurocognitive disorder; Geriatric psychiatry; Cognitive decline

s/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 16, 2020
Peer-review started: December 16, 2020
First decision: April 6, 2021
Revised: May 10, 2021
Accepted: June 28, 2021
Article in press: June 28, 2021
Published online: July 19, 2021

P-Reviewer: Chakrabarti S
S-Editor: Zhang L
L-Editor: A
P-Editor: Li JH

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Core Tip: Practicing clinicians should utilize validated measures when screening for cognitive impairment among older adults. Based on their findings they should make recommendations for further evaluation and not use cognitive screening tools as diagnostic tools.

Citation: Rose AF, Gilbertson AF, Cottrell C, Tampi RR. Cognitive screening for adult psychiatric outpatients: Comparison of the Cognivue® to the Montreal Cognitive Assessment. *World J Psychiatr* 2021; 11(7): 265-270
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/265.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.265

INTRODUCTION

Cognitive decline is the leading cause of functional impairment among older adults [1]. As the population of older adults in the United States continues to rise, recognition and prevention of neurocognitive disorders becomes increasingly important. Screening for cognitive deficits facilitates early identification of these disorders, which, in turn, helps providers determine when to refer patients to neurology, psychology, or geriatric specialists for more extensive evaluation. Further, recognition of cognitive impairments allows clinicians to more effectively monitor safety and adherence to treatment, determine when to include family in treatment/decision making, and make accommodations during visits (such as providing materials and instructions the patient can understand and remember). Early and accurate diagnosis enables clinicians to educate patients and their families on symptoms and prognoses and to advise on treatment and support options.

There are different types of neurocognitive disorders (*i.e.*, mild and major) that vary in symptom presentation, degree of impairment, prognosis, and treatment. Screening for and differentiating among these conditions can be a challenge. When testing for cognitive impairments, an ideal screening tool should sample the various cognitive domains that are most often compromised. These domains include executive functioning, visuospatial skills, language, processing speed, attention, memory, abstraction, and psychomotor skills[2]. In addition to using the cognitive screening tool, direct observation of the patient and collection of collateral information from a close family member, friend, or caregiver can provide important details regarding symptoms and level of functioning. This information will assist clinicians in making informed decisions on how to proceed with further evaluation and treatment. Clinicians should not rely solely on cognitive screening tools to diagnose patients with neurocognitive disorders, as gathering additional information is imperative in confirming a diagnosis and providing the most appropriate treatment for patients. Incorrectly diagnosing any type of neurocognitive disorder can lead to mismanagement of symptoms, improper use of medications, anxiety and distress for patients and their families, and unnecessary health care costs.

CRITICAL EVALUATION OF SCREENING INSTRUMENTS

It is important to critically evaluate screening tools to ensure they are psychometrically valid. Currently, there are a number of readily available screening instruments from which to choose[3]. Among the more widely researched and utilized screeners are the montreal cognitive assessment (MoCA), saint louis missouri mental status (SLUMS), and mini-mental state examination (MMSE). The MoCA detects symptoms of dementia with 100% sensitivity and 87% specificity[4]. It has been shown to evaluate many cognitive domains that are impacted in the various types of neurocognitive disorders. The pen-and-paper tool is administered by a clinician and takes about 10 min to complete. Scores range from 0-30 (+1 for 12 or fewer years of education); a score of 26 or higher indicates "normal" cognitive functioning, while a score of 25 or lower indicates "impaired" functioning.

Cognivue® is a recently introduced screening tool that is administered using a standalone computer and onscreen instructions. The instrument has been "cleared" by the Food and Drug Administration (FDA), signifying that the administration does not perceive it to pose any danger to patients when used as directed[5]. Notably, clearance of a "de novo medical device" implies there is no comparable instrument and, thus, imposes few, if any, requirements for comparative analyses. Cognivue® provides scores ranging from 0-100, with a score of 75 or higher signifying "normal" cognitive functioning, a score of 51-74 signifying low-moderate cognitive impairment, and a score of 50 or lower signifying severe cognitive impairment. There are a few research studies on this device which have been company-funded and focused on comparing Cognivue® results with that of the SLUMS and several other neuropsychological assessment tools. This research by Cahn-Hidalgo *et al*[6] was published in a recent issue of the *World Journal of Psychiatry* [2020; 10(1); 1-11].

In the Cahn-Hidalgo *et al*[6] article they noted correlations between various neuropsychological tests and the "components" of the Cognivue®; however, it is unclear which subtests of the Cognivue® fell under each of the five "components". It did label the components as verbal processing, manual dexterity and speed, visual acuity, visuospatial and executive function, and speed and sequencing, which doesn't align with the domains on the clinician report generated by the Cognivue® (*i.e.*, Visuospatial, Executive Function/Attention, Naming/Language, Memory, Delayed Recall, and Abstraction). The results from Table of their article highlight strong correlations (0.529 to 0.902) between verbal processing and the SLUMS naming task and Rey Auditory Verbal Learning Test; manual dexterity and speed with Groove Peg Board Task; visuospatial and executive function with Trails B and Judgment of Line Orientation; and speed and sequencing with Trails A (Cahn-Hidalgo *et al*[6], 2020). Correlations with other Cognivue® components and neuropsychological tests administered had low to moderate correlations (0.003 to 0.408) also outlined in Table. There was no good indication in this research that the Cognivue® tapped into the domains of attention, immediate memory, delayed recall, or abstraction, which are important areas to consider when screening for neurocognitive disorders. For example Cognivue® presentation of stimuli is all visual, which is a limitation. After initial exposure a few seconds pass before the participant is given a multiple choice paradigm to recognize and respond. This brief delay can be categorized as a short-term memory process, but not a long-term memory one. Additionally when considering models of memory, recognition of stimuli in a multiple choice format is easier than free recall of information or encoding the stimuli to long-term memory[2]. Since recognition can be intact in some individuals with neurocognitive disorders, such as with vascular dementia or mild cognitive impairment, presentation of information in this way could lead to false-negatives. Additionally it is unclear how the Cognivue® subtests measure executive functioning skills even though Cahn-Hidalgo *et al*[6] research suggests correlations with Trails B, an executive function test.

It is also important to highlight that correlations between subtests do not necessarily mean that they are valid or even that they measure the intended variables. For example, the naming task on the SLUMS had a strong correlation (0.529) with the "language" measures on Cognivue®[6]. The SLUMS naming task requires the subject to verbally generate as many animals as they can in one minute and is intended to screen for aphasia and other language/speech disturbances. In comparison, the language section on Cognivue® does not have a verbal component. The tasks consist of single letters or simple three-letter words being visually displayed on a screen and then presents the subject with a visual multiple-choice paradigm, which requires them to select what was previously presented from items that were not. While this task involves some elements of language, it does not assess the same area of the brain as a naming task that requires verbal fluency and word finding skills, which are commonly observed deficits in neurocognitive disorders like Alzheimer's disease[2]. The cognitive domains measured by the Cognivue® are not well defined or researched in comparison to other screeners and neuropsychological measures.

Importantly, there are potential conflicts of interest with the aforementioned article. The research was funded by the makers of Cognivue® and the authors were employees or consultants for the company. Therefore it is important that studies with larger sample sizes are completed by unaffiliated researchers for validation of the Cognivue®. Additionally the company did not use trained psychologists or clinicians to administer the neuropsychological assessments in their research, calling the validity of the results into question. These authors concluded that the Cognivue® is either the equivalent or superior to the SLUMS when screening for cognitive impairment and "superior" for test-retest reliability[6,7]. They do admit more comparison studies are warranted; however they go on to infer that the Cognivue® will be equivalent in terms

Table 1 Demographics and montreal cognitive assessment and Cognivue® Scores

	Positive MoCA score, *n* = 12	Positive Cognivue® score, *n* = 12
Gender, *n* (%); Male; Female	5, (41.7); 7 (58.3)	0, (0.0); 12 (100.0)
Age, yr	63.1 (5.0)	68.0 (7.2)
Length of education, yr	15.5 (2.2)	15.4 (2.4)
MoCA score	24.3 (0.8)	27.1 (1.3)
Cognivue® score	81.3 (4.7)	62.7 (11.6)

Presented as mean (SD), unless otherwise indicated. MoCA: Montreal cognitive assessment.

of its sensitivity, specificity, and psychometric validity to commonly used screeners like the MoCA and MMSE[6]. Without more research, with larger sample sizes, it is not appropriate to suggest the Cognivue® is more useful or accurate than other screening instruments. Furthermore the researchers claim the Cognivue® reduces "costs" associated with screening for cognitive impairments; however the cost saving advantage of this device *vs* other tools has not been established.

Unfortunately there are limited validation studies of the Cognivue®, especially ones that are not associated with or funded by the company. There has been research examining the use of the Cognivue® with a small sample of MS patients, which was coauthored by the founder and chief executive officer of Cerebral Assessment Systems and inventor of Cognivue®. This study compared Cognivue® total scores to the paced auditory serial addition test (PASAT) (which assesses auditory information processing speed, attention, and flexibility) and symbol digit modalities test (SDMT) (which assesses visual processing speed and attention)[8]. The PASAT and SDMT are commonly used cognitive screeners and research tools when working with Multiple Sclerosis (MS) patients[9]. Smith *et al*[8] found strong correlation between the Cognivue® Total Score and SDMT (0.79) and the PASAT (0.61)[8]. In 2020 Bomprezzi expanded this research and found moderate correlations (0.67) between the Cognivue® Total Score and SDMT results in a small sample of MS patients[10]. The finding of these studies suggests the Total Cognivue® score correlates with tests that are measuring elements of attention and processing speed.

Digital and computer based screeners and tests show promise for detecting cognitive impairments[11]. In addition to the Cognivue® there has been development of different computerized cognitive screeners. For example the historical Clock Drawing Test has been transformed into a digital version. The five minute Digital Clock Drawing Test is registered as a FDA Class II medical device for cognitive screening[12]. The tablet uses a digitizing pen that captures and analyzes the drawing. One Harvard research study concluded the DCT clock showed "excellent discrimination" between individuals with cognitive impairment and controls[12]. Unfortunately much of the technology and test adaptations for these devices are new, with few studies, small sample sizes, and lack of evidence, making it risky to suggest that computerized testing should be used clinically for the detection, diagnosis, and monitoring of neurocognitive disorders without complete and validated research[11].

We compared the Cognivue® to the MoCA to assess its ability to screen for cognitive deficits among older adults in a mental health outpatient clinic. Both instruments were administered to 58 adult clinic outpatients aged 55-89 years by trained personnel. The results showed 28% agreement between tests for patients who did not screen positive for cognitive impairment according to their scores. In contrast, 42 (72%) patients screened positive on one or both measures. Of all patients who screened positive, the tests showed only 43% agreement in terms of identifying patients who may benefit from further assessment. Both Cognivue® and the MoCA independently identified 12 different patients as being positive for cognitive impairment. Demographics as well as MoCA and Cognivue® scores are described in Table 1. As can be seen here, there may be particular risks for false positive results among older women using Cognivue® and among patients who score close to the cutoff (24 or 25) using the MoCA.

Given the lack of agreement between these measures, we then determined whether correlations exist between domains of the MoCA and Cognivue® and whether Cognivue® measures the same or similar domains as the well-established MoCA. The results, presented in Table 2, suggest there are a few low to moderate correlations between subtests of the two instruments, in terms of ability to assess visuospatial abilities, naming ability, and attention. The results also indicated that most subtests,

Table 2 Correlations between Subtests of the montreal cognitive assessment and Cognivue®

MoCA subtests	Cognivue® subtests	Correlation score	*P* value
Executive function/visuospatial	Cognivue visual salience	0.24815	0.0604
Executive function/visuospatial	Cognivue shape discrimination	0.26059	0.0482
Executive function/visuospatial	Cognivue motion discrimination	0.30570	0.0196
Executive function/visuospatial	Cognivue word memory	0.19058	0.1519
Executive function/visuospatial	Cognivue shape memory	0.35760	0.0059[1]
Attention	Cognivue visual salience	0.43944	0.0006[1]
Attention	Cognivue share discrimination	0.19740	0.1375
Attention	Cognivue motion discrimination	0.34035	0.0089
Attention	Cognivue word memory	0.25763	0.0509
Attention	Cognivue shape memory	0.42319	0.0009[1]
MoCA naming	Cognivue letter discrimination	0.44421	0.0005[1]
MoCA naming	Cognivue word discrimination	0.35821	0.0058[1]
MoCA language	Cognivue letter discrimination	0.28987	0.0273
MoCA language	Cognivue word discrimination	0.09739	0.4670
MoCA delayed memory	Cognivue word memory	0.30907	0.0182
MoCA delayed memory	Cognivue shape memory	0.21664	0.1024
MoCA delayed memory	Cognivue letter memory	0.27064	0.0399
MoCA delayed memory	Cognivue motion memory	0.29831	0.0229
MoCA delayed memory	Cognivue word discrimination	0.19972	0.1328
MoCA delayed memory	Cognivue shape discrimination	0.30308	0.0207
MoCA abstraction	Cognivue shape discrimination	-0.03896	0.7715
MoCA abstraction	Cognivue motion discrimination	0.00276	0.9836

Bolded numbers represent significant correlations between the subtests.
[1]Notes it was significant at the $P < 0.005$ level.
MoCA: Montreal cognitive assessment.

which purportedly measure the same domains, do not demonstrate commensurate correlations.

CONCLUSION

The findings of this limited study raise questions regarding the utility of Cognivue® for its intended purposes. We compared instruments and based on our findings and previous research which determined that the MoCA is the preferable screening tool. While both instruments seemed comparable with regard to their acceptability to patients, the MoCA does require more time from trained personnel to administer. In addition, the use of MoCA is now restricted to trained users as there were significant variations observed in the quality of the tests that were administered and the potential liability that this issue causes to its users[13]. The training to administer and score the MoCA has been deemed necessary starting September 1, 2019. The users will have 1 year to complete their training and will continue during that time to access the test without any restriction. After September 1, 2020, the access to the test has been restricted to certified users. We believe the requirement of additional time is offset by the extensive body of research supporting its psychometric properties and the significant risks to patients when screeners result in misdiagnosis.

Our findings call into question claims pertaining to the domains that Cognivue® measures, which are crucial for correctly identifying potential neurocognitive deficits. Most Cognivue® subtests appear to place cognitive demands in the domains of visual

ability, motor control, attention, processing speed, visual discrimination, and short-term memory/recognition. These areas are important; however, if patients have deficits in one or more of these domains, it may impact their performance on some, if not all, subtests of the Cognivue® given the way tasks are presented. Therefore, results may be skewed, potentially creating false positive outcomes. Additionally the subtests do not appear to assess long-term memory, executive functioning, language, or abstraction. Clearly defining the subtests of the Cognivue® is crucial in determining its efficacy as a screening tool. More research by unaffiliated researchers, on large samples of participants, is needed to determine what specifically the Cognivue® subtests are measuring and what modifications can be made to improve its screening capabilities.

Practicing clinicians should be aware of the importance of identifying cognitive impairments among older adults. Screening tools may play an important role in the identification of cognitive impairments and should not be seen as an inconvenience, but as an essential part of optimizing patient care. A cognitive screening tool should not be chosen because it is new and easily administered, but because it is the most efficacious way to accomplish the task. We recommend that clinicians primarily use the MoCA for this purpose. Further, we propose that use of Cognivue® be evaluated carefully, until its subtests are modified or more research proves that the test meets standards for reliability and validity. Inadequate evaluation and misdiagnosis of neurocognitive disorders can be distressing for patients and their families and lead to inappropriate treatment and unnecessary healthcare costs. It is important to remember that a cognitive screening tool should not be used in isolation to establish a diagnosis of neurocognitive disorder, rather, it should be used to assist clinicians in determining when further evaluation is indicated.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 271-276

DOI: 10.5498/wjp.v11.i7.271

ISSN 2220-3206 (online)

OPINION REVIEW

Primary care and mental health: Where do we go from here?

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Author contributions: Moise N and Shah RN contributed study concept and design; Moise N, Shah RN and Wainberg M contributed acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of manuscript for important intellectual content and statistical analysis; Moise N obtained funding and contributed study supervision.

Supported by National Institute of Mental Health Agency for Healthcare Research and Quality (AHRQ), No. R01HS025198 (to Moise N).

Conflict-of-interest statement: Shah RN is a clinical advisor with < 1% equity interest in the following mental health startups which were not involved in the conduct of this study: Two Chairs, Groupwell, Mantra Health, and Tempest. The other authors declare that they have no competing interests.

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Abstract

Primary care has been dubbed the "de facto" mental health system of the United States since the 1970s. Since then, various forms of mental health delivery models for primary care have proven effective in improving patient outcomes and satisfaction and reducing costs. Despite increases in collaborative care implementation and reimbursement, prevalence rates of major depression in the United States remain unchanged while anxiety and suicide rates continue to climb. Meanwhile, primary care task forces in countries like the United Kingdom and Canada are recommending against depression screening in primary care altogether, citing lack of trials demonstrating improved outcomes in screened *vs* unscreened patients when the same treatment is available, high false-positive results, and small treatment effects. In this perspective, a primary care physician and two psychiatrists address the question of why we are not making headway in treating common mental health conditions in primary care. In addition, we propose systemic changes to improve the dissemination of mental health treatment in primary care.

Key Words: Mental health; Collaborative care; Primary care; Depression; Integrated care; Anxiety

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United States

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 1, 2021
Peer-review started: March 1, 2021
First decision: April 20, 2021
Revised: April 30, 2021
Accepted: June 15, 2021
Article in press: June 15, 2021
Published online: July 19, 2021

P-Reviewer: Gazdag G, Tung TH
S-Editor: Gao CC
L-Editor: A
P-Editor: Li JH

Core Tip: Primary care has been dubbed the "de facto" mental health system of the United States since the 1970s. Two psychiatrists and an internist at a major academic medical center review difficulties with implementation of collaborative care in academic primary care settings along with novel recommendations to improve dissemination of this evidence based practice.

Citation: Moise N, Wainberg M, Shah RN. Primary care and mental health: Where do we go from here? *World J Psychiatr* 2021; 11(7): 271-276
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/271.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.271

INTRODUCTION

Much of the evidence for integrating mental health treatment into primary care settings comes from collaborative care (CC) interventions for depression. While the effect of CC on clinical outcomes like glycemic control has been inconsistent[1], CC has proven effective in improving depressive symptoms, satisfaction, quality of life and costs[2,3], especially among racial and ethnic minorities[4]. Policymakers and researchers designed CC to optimize the care of psychiatric patients, the majority of whom receive mental health treatment in primary care. The last decade saw remarkable improvements in CC implementation and reimbursement[5]. However, the recent coronavirus disease 2019 (COVID-19) pandemic contributed to physical morbidity and mortality but also social isolation, loneliness, economic insecurity, and alarming rates of acute stress, anxiety, and depression among patients[6] and providers alike[7]. Depression for example increased 3-fold in the United States[8], and up to 7-fold according to recent meta-analysis of multiple countries[9]. Few if any recent articles have addressed how best to overcome barriers to CC implementation in the post-COVID era, however. In this perspective, we address emerging barriers and challenges to treating common mental health conditions. In addition, we propose systemic changes to improve the dissemination of mental health treatment in the telemedicine era.

CHALLENGES PRIMARY CARE PHYSICIANS FACE IN TREATING MENTAL HEALTH

Policymakers, providers and researchers developed CC models, in part, to address gaps in the access to quality mental health treatment in primary care and to offload busy primary care providers (PCPs). The lynchpin of these models are care managers, typically nurses or licensed social workers, who provide monitoring (using standardized screening tools) and problem-solving therapy under the supervision of a psychiatrist who assists with case review and complex cases. It remains unknown whether the programs can handle or even effectively treat the new deluge of patients with mental health issues. In fact, studies from multiple countries conducted in 2020 (53 studies; n = 158000) report high point prevalence estimates of stress (29%-31%), depression (25%-47%), anxiety (32%-47%), sleep disturbances (34%-36%), and posttraumatic stress disorder (16%-18%)[9-17].

At the systems level, even prior to COVID-19, settings with CC programs reported insufficient resources (*e.g.*, care manager fulltime equivalents) to address the volume and complexity of common mental health disorders seen in real-world primary care settings[18]. This remains an issue despite inroads in payment models and an expanded non-physician workforce. There are a variety factors contributing factors to the insufficient number of care managers to meet patient demand, including low reimbursement rates, limited time due to competing demands (*i.e.*, coordination *vs* therapy), low job satisfaction, and suboptimal relationships with PCPs, particularly in large primary care settings with numerous PCPs per care manager[18]. Relatedly, CC outcomes also hinge on having a strong, integrated primary health care system[5], which has also historically been difficult to widely implement[19]. Furthermore, the rapid uptake of telemedicine during the COVID-19 pandemic affected clinical roles,

particularly for medical assistants who traditionally administered depression screening but lack pre-visit telemedicine workflows. Meanwhile, communication infrastructures among staff, patients, and providers have become fragmented. Due to the economic effects of COVID-19, many medical settings now have a greater percentage of uninsured, Medicare and Medicaid patients and higher costs on a case-mix adjusted basis. Few studies, however, examine the unique barriers to CC implementation in settings that operate in fee-for-service models that devalue mental health care[18].

Provider engagement is also crucial to CC implementation[18,20], but PCPs increasingly face shortened, now remote, visits, administrative/teaching/telemedicine onboarding tasks, high turnover (*i.e.*, of trainees) as well competing quality improvement priorities (*e.g.*, diabetes targets, domestic violence screening), all resulting in fatigue and burnout[18]. Many providers in academic settings are not always physically present in clinics (*e.g.*, have half day sessions) and lack formal mental health/CC training in residency, producing physicians ill-equipped to successfully manage their patients' mental health conditions and provide population health-based 'shared-care' with a psychiatrist[21]. Increasing rates of provider psychological distress may also make it difficult to detect and address mental health issues in patients[7]. Finally, direct communication between PCPs and psychiatrists remains rare in these models despite the fact that physician-to-physician engagement often fosters a medical learning environment that enhances the psychiatric treatment skills of PCPs. This may explain why even successfully implemented CC programs see remission in less than half of patients[22].

Meanwhile, patient level barriers include stigma, fear of side-effects, low treatment availability and preferences for focusing on physical concerns resulting in patient nonadherence[23], which is compounded by chronic, resistant, psychosomatic symptoms often seen in primary care settings. It's unclear whether the mental but also long-term physical sequelae of COVID-19 can be effectively managed by the short-term treatment provided by CC.

ROLE DISCORDANCE: CHALLENGES FOR PSYCHIATRISTS

Integrated care models require psychiatrists to step back from direct patient care and collaborate with a care manager who provides therapy and communicates with the PCP for medication management. Although in an idealized CC setting, psychiatrist time would be focused on educating the team and supervising the care manager, often the psychiatrist's limited time quickly becomes filled with direct patient consults. This is the result of several factors. Psychiatry residency, like all the other medical residency training programs, offers little if any training in supervising other clinicians (*e.g.*, care managers) or liaising with PCPs during psychiatry residency. Concrete data does not exist to dictate whether a patient would be better suited for independent care by the PCP as opposed to direct or indirect (*via* care manager) psychiatric consultation, resulting in a patchwork of unnecessary psychiatric consultations or patients remaining in primary care who need referral to more specialized treatment. In addition, like in most other specialty residency training programs, many physicians enter psychiatry specifically to spend time delivering individual care to patients, creating a tendency to veer towards direct *vs* indirect consultation. Combined with the general psychiatrist workforce shortage, these factors make locating psychiatrists for these roles challenging. Finally, while the advent of telepsychiatry comes with improvements in access and convenience for patients and providers, corresponding decreases in direct face-to-face interaction with PCPs and care managers can create unique challenges, such as reduction in non-verbal cues and informal interactions that are often necessary for clarifying clinical and process details and building team-based trust and rapport[24].

LEVERAGING ADVANCES IN MENTAL HEALTH AWARENESS AND TREATMENT TO ADDRESS PRIMARY CARE NEED IN THE POST-COVID ERA

In the post-COVID era, telehealth both for primary care and mental health is increasingly the norm and will at least partially remain in place, offering a rare opportunity to address the above barriers and expand and improve the delivery of CC

for mental disorders in primary care. Prior research suggests that off-site telemedicine-based CC may yield better outcomes than local practice-based CC albeit through better fidelity[25], but widespread implementation will require innovative, multi-disciplinary solutions and adaptations. In Table 1, we recommend several interventions to improve mental healthcare in the primary care setting, starting with requiring dedicated time during outpatient internal medicine residency rotations to learn psychopharmacological and CC principles but also self-care strategies for reducing provider burnout. The Advancing Integrated Mental Health Solutions Center is a valuable resource for CC training. In addition, groups like the Association of American Medical Colleges have begun to create online curricula and modules for residents, and topics include cognitive behavioral therapy for insomnia and trauma informed care. Second, telemedicine era primary care settings may benefit from leveraging technology to make psychoeducation, cognitive behavior therapy (CBT) apps, and symptom self-monitoring, all proven effective in prevention and/or managing mild symptoms, part of routine care[26] (perhaps as part of new pre-visit telehealth roles of medical assistants or patient portals). This may be particularly important given the deluge of patients with mental health concerns in the post-COVID-19 era[6]. The American Psychiatric Association developed toolkits of telepsychiatry and CBT apps, which will be important resources.

Regardless, medication and therapy remain first-line in moderate-severe cases[26]. Patient-preference driven or precise, individualized algorithms (*e.g.*, machine learning) for targeting screening and treatment according to patient depression phenotypes or risk[27] is now possible with integrated electronic health records and may further help address resource limitations, patient engagement and treatment efficiency. In CC settings, improved designations for referrals to care management *vs* direct psychiatry, ideally both remotely delivered, will also be essential and improve efficiency and engagement. Care will need to be taken to avoid technology-driven disparities among the socioeconomically disadvantaged populations often seen in community and academic medical centers (*e.g.*, addressing concerns with stigma and confidentiality; offering phone *vs* video visits). True inroads in mental health treatment in primary care will require flexibility and acknowledging that not every setting is suitable for CC and may instead benefit from improving psychiatry-PCP communication, particularly in non-integrated medical settings where collaboration remains siloed[28]. Advances in telemedicine and technology have the potential to improve communication and make "colocation" even more possible, particularly in settings where a higher density of PCPs and psychiatrists practice.

DISSEMINATING SKILLS FOR PSYCHIATRISTS WORKING IN PRIMARY CARE

While the Accreditation Council for Graduate Medical Education-required experience in consultation-liaison psychiatry provides some inpatient training in collaboration, the outpatient environment is meaningfully different. Trainees need practice and supervision to know the limits of what can and cannot be done with a patient they have not directly interviewed, and how to teach colleagues clinical pearls in a digestible and helpful manner. These skills can and should be part and parcel to psychiatric training. In the interim, the American Psychiatric Association has developed trainings for psychiatrists already in practice to learn the skills needed to successfully operate in a CC setting. Systems should compensate psychiatrists not only for direct patient time but also indirect consultations and teaching primary care colleagues the nuances antidepressant titration strategies. These are the tools that will help scale an expertise-driven treatment of depression and anxiety much faster than having these patients wait to see a psychiatrist. Relatedly, financial models now compensate for telepsychiatry and tele-CC models but should also align with the long-term need for indirect e-consultations as well as with new roles of PCPs and psychiatrists within integrated care settings particularly in the post-COVID-19 financial milieu.

CONCLUSION

In conclusion, long-standing barriers to addressing mental health in primary care settings are underscored in today's environment. COVID-19 propelled the use of

Table 1 Recommendations to improve treatment of common mental health conditions in primary care settings

Recommendations
(1) ACGME requirements should be amended to require dedicated time for primary care physicians to learn self-care/burnout prevention as well as basic problem-solving therapy and psychopharmacological care on outpatient psychiatry rotations or through internal medicine resident-run mental health clinics and for psychiatrists to learn how to supervise other clinicians, including but not limited to: social workers, psychologists, and primary care doctors who function as the primary prescribers; (2) Health systems should streamline communications systems (pagers, cellphones, telehealth) to create access to e-consultations for primary care doctors needing psychiatric expertise; (3) Financial models should align with the long-term need for indirect consultations as well as with new roles of primary care providers and psychiatrists within integrated care settings particularly in the post-COVID-19 financial milieu; (4) Integrated care models should leverage technology to fill administrative functions (such as tracking patient health questionnaire (PHQ-9 forms), develop guidelines for determining when and how to use smartphone treatment applications and self-care resources in primary care settings, and rapidly expand telemedicine to address workforce gaps particularly in socioeconomically disadvantaged groups who face technology-driven disparities; (5) Primary care practices must partner with psychiatry specialty services to create a robust process for referring appropriate patients to specialty mental health care; and (6) Real world effectiveness research should be conducted to elucidate the effectiveness of precisely and efficiently targeting screening and treatment recommendations according to patient phenotype, risk and preference

ACGME: Accreditation Council for Graduate Medical Education; COVID-19: Coronavirus disease 2019.

telehealth and telepsychiatry, offering multiple opportunities for improving the uptake of CC. Future success in these settings will require that primary care and mental health providers apply lessons learned during this period and consider innovations in training, technology, workforce, and treatment selection.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 277-296

DOI: 10.5498/wjp.v11.i7.277

ISSN 2220-3206 (online)

REVIEW

Novel approaches in schizophrenia-from risk factors and hypotheses to novel drug targets

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Author contributions: Ľupták M wrote a part of MS regarding genetics, stress and triggers of schizophrenia; Fišar Z wrote current hypotheses of schizophrenia; Michaličková D wrote immunologic processes in schizophrenia; Hroudová J wrote novel strategies for treatment of schizophrenia and completed the MS; all authors approved the final version.

Supported by the Projects Progres of Charles University, No. Q25/LF1 and No. Q27/LF1; the Grant Agency of Charles University, Czech Republic, No. 34119; and the Project Ministry of Health, Czech Republic for Conceptual Development of Research Organization, No. 64165.

Conflict-of-interest statement: Authors declare that there is no conflict of interest regarding the publication of this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external

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Abstract

Schizophrenia is a severe psychiatric disorder characterized by emotional, behavioral and cognitive disturbances, and the treatment of schizophrenia is often complicated by noncompliance and pharmacoresistance. The search for the pathophysiological mechanisms underlying schizophrenia has resulted in the proposal of several hypotheses to explain the impacts of environmental, genetic, neurodevelopmental, immune and inflammatory factors on disease onset and progression. This review discusses the newest insights into the pathophysiology of and risk factors for schizophrenia and notes novel approaches in antipsychotic treatment and potential diagnostic and theranostic biomarkers. The current hypotheses focusing on neuromediators (dopamine, glutamate, and serotonin), neuroinflammation, the cannabinoid hypothesis, the gut-brain axis model, and oxidative stress are summarized. Key genetic features, including small nucleotide polymorphisms, copy number variations, microdeletions, mutations and epigenetic changes, are highlighted. Current pharmacotherapy of schizophrenia relies mostly on dopaminergic and serotonergic antagonists/partial agonists, but new findings in the pathophysiology of schizophrenia have allowed the expansion of novel approaches in pharmacotherapy and the establishment of more reliable biomarkers. Substances with promising results in preclinical and clinical studies include lumateperone, pimavanserin, xanomeline, roluperidone, agonists of trace amine-associated receptor 1, inhibitors of glycine transporters, AMPA allosteric modulators, $mGLUR_{2-3}$ agonists, D-amino acid oxidase inhibitors and cannabidiol. The use of anti-inflammatory agents as an add-on therapy is mentioned.

Key Words: Schizophrenia; Immune system; Inflammation; Genetics; Novel antipsy-

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Czech Republic

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 27, 2021
Peer-review started: February 27, 2021
First decision: March 30, 2021
Revised: April 6, 2021
Accepted: June 18, 2021
Article in press: June 18, 2021
Published online: July 19, 2021

P-Reviewer: Zhang Y
S-Editor: Zhang H
L-Editor: A
P-Editor: Xing YX

chotics; Add-on therapy

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Core Tip: This review discusses the newest insights in the pathophysiology and risk factors for schizophrenia and points out the novel approaches of antipsychotic treatment, potential diagnostic and theranostic biomarkers. The hypotheses focusing on neuromediators (dopamine, glutamate, serotonin), neuroinflammation, cannabinoid hypothesis, gut brain axis model, and other currently discussed hypotheses are summarized. Key genetic features and new findings in the pathophysiology of schizophrenia support the expansion of novel approaches in pharmacotherapy and development of non-dopaminergic antipsychotics.

Citation: Ľupták M, Michaličková D, Fišar Z, Kitzlerová E, Hroudová J. Novel approaches in schizophrenia-from risk factors and hypotheses to novel drug targets. *World J Psychiatr* 2021; 11(7): 277-296
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/277.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.277

INTRODUCTION

Schizophrenia is a serious mental disorder with a lifelong prevalence of approximately 1% and a peak age of onset of 23-34 years in women and the early twenties in men. It is a very complex syndrome that involves widespread brain multi-dysconnectivity. It is characterized by cognitive, behavioral and emotional dysfunctions. To fulfil the diagnostic criteria for schizophrenia, patients must exhibit two or more negative, disorganized or positive symptoms that persist for a minimum of six months, and at least one symptom must be disorganized speech or a positive symptom[1]. Positive symptoms include hallucinations and delusions; negative symptoms are characterized by deficits in normal behavior, including asociality, alogia, anhedonia, blunted affect, and avolition[2]. There is a wide range of treatment possibilities; however, the effectiveness and/or adverse effects of antipsychotics with different pharmacological profiles vary. Successful treatment of schizophrenia is complicated by noncompliance and pharmacoresistance. The prevalence of pharmacoresistant schizophrenia is estimated to range from 12.9% to 48%[3]. It has been estimated that approximately 20% of patients with schizophrenia receive combination treatment and/or antipsychotic polypharmacy[4]. Augmentation strategies used in clinical practice include the addition of another antipsychotic, concurrent administration of benzo-diazepines or mood stabilizers, repetitive transcranial magnetic stimulation or electroconvulsive therapy.

The pathophysiological mechanism of the onset and progression of schizophrenia, the diagnostic neuropathology, and sensitive and specific biomarkers have not yet been identified. Several different hypotheses have been proposed to explain the neuropathology of schizophrenia that focus on environmental, genetic, neurodevelopmental, and neurochemical effects. Research and development in imaging methods and in preclinical studies have led to the improvement of these theories. Positron emission tomography (PET) and single photon emission computer tomography enable *in vivo* quantification of dopaminergic functions in the brain and dopamine synthesis, release, and availability in postsynaptic dopaminergic neurons and transporters.

The targeting of existing and new drugs is based primarily on the dopamine and glutamate hypotheses of schizophrenia. All current antipsychotics modulate the function of the dopamine D_2 receptor. A nonlinear relationship between D_2 receptor occupancy, clinical response, and adverse effects of current antipsychotics was found. A small response to antipsychotic treatment appears at 50% dopamine receptor occupancy; as receptor occupancy increases, the response increases as well as the risk of extrapyramidal adverse effects[5]. These findings were proven in a double-blind study in patients with first episode schizophrenia; 65% occupancy of D_2 receptors was the borderline between responders and nonresponders[6]. Recently, research has focused on the prodromal phase of schizophrenia. Dopamine synthesis increases

during the acute phase of the disease. Stress and other risk factors affect the dopamine systems, leading to their dysregulation and consequently to the development of psychotic disorder[7].

Excitatory glutamate neurotransmission occurs though ionotropic and metabotropic glutamate receptors. The glutamate hypothesis of schizophrenia is based on the dysfunction of the N-methyl-D-aspartate (NMDA) receptor. Currently, the effects of ketamine on brain function in healthy volunteers are being examined; studies are focused on glutamate concentrations in the brains of patients with prodromal symptoms during the first episode and other episodes of schizophrenia. Dysfunction of both NMDA receptors and presynaptic synthesis of dopamine has been implicated in the clinical symptoms of schizophrenia. Relationships between presynaptic dopamine dysfunction and positive symptoms and between glutamate dysfunction and negative and cognitive symptoms are expected[7].

To improve the diagnosis of schizophrenia, predict the therapeutic response to antipsychotics, develop new drugs, and personalize treatment, it is necessary to identify new specific and sensitive biomarkers of the disease[8]. Blood-based biomarkers are regarded as a feasible option because the dysregulation of gene expression, epigenetic patterns, protein quantities, and metabolic and inflammatory molecules in peripheral blood have been shown to have distinct patterns in patients with schizophrenia[8]. The aim of this review is to provide the newest insights into the pathophysiology and risk factors of schizophrenia and novel approaches to antipsychotic treatment.

GENETICS AND SCHIZOPHRENIA

Schizophrenia is closely linked to genetic factors, including small nucleotide polymorphisms (SNPs), copy number variations and changes in gene expression. Combinations of different pathogenic mechanisms, including aberrant DNA methylation, altered histone code, dysregulated long noncoding RNA (lncRNA)-dependent tethering of epigenetic complexes to DNA, aberrant polyadenylation of pre-mRNAs, and mis-splicing, have been reported to play a role in schizophrenia development[9]. The hereditary burden of schizophrenia is estimated to be approximately 80%. Genome-wide association studies (GWAS) have identified more than 100 loci, many of which contain multiple genes that are significantly associated with schizophrenia. The assessment of polygenic scores allows us to determine the risk of schizophrenia based on the number of risk alleles weighted by the odds ratio of each allele.

DNA methylation, an epigenetic process that produces 5-methylcytosine, is mediated by DNA methyltransferases and has a key role in several processes, such as imprinting, inactivation of the X-chromosome, silencing of transposons or regulation of genomic stability and chromatin structure. Schizophrenia is linked to pathophysiological DNA methylation of several genes, including those encoding reelin, catechol-O-methyltransferase (COMT), monoamine oxidase A, serotonin receptor 2A, the transcription factor SOX-10, and others. Unfortunately, no schizophrenia-specific "methylation panel" has been proposed, and it has not yet been clarified whether these changes represent causes or consequences of schizophrenia development[9].

Approximately 70%-80% of the genome is transcribed into noncoding transcripts, and the majority of schizophrenia-associated risk variants have been found in noncoding regions. LncRNAs can interact with DNA, RNA, and proteins, influencing transcription and posttranscriptional processes such as splicing, polyadenylation and/or regulation of transcript stability. MicroRNAs (miRNAs) are small noncoding RNAs that regulate more than 50% of protein-coding genes by acting as promoter or enhancer elements; miRNAs might participate in histone, DNA, or chromatin methylation and modification. Both lncRNAs and miRNAs can be affected by different genetic variants, especially SNPs, which could increase the risk of schizophrenia onset [9,10].

Microdeletions in chromosomal region 22q11.2 are one of the well-established genetic risk factors for schizophrenia and increase the risk of schizophrenia development to 30%-40%[11,12]. COMT is a major dopamine catabolic enzyme, and its gene is located in this microdeletion region. In addition, a functional COMT polymorphism [valine/methionine (VAL/MET) substitution at codon 108] causes differences in its catabolic activity, dopamine baselines and stress-induced cortical dopamine release[13]. The MET version of the allele is not as stable as the VAL version, causing decreased COMT activity and an increase in dopamine levels,

especially in the prefrontal cortex[14].

The major histocompatibility complex (MHC) locus located on chromosome 6, which contains genes encoding proteins essential for adaptive immunity, has one of the strongest links to schizophrenia. Specifically, there was increased expression of complement component 4A (C4A). Sex differences in the *C4* gene could explain the higher male susceptibility to schizophrenia. Schizophrenia patients with higher C4 Levels were characterized as low responders or nonresponders to antipsychotic medication. The expression of the genes encoding CSMD1 and CSMD2, which are important regulators of C4, has been found to be decreased in schizophrenia and connected with reduced cognition and executive function[15,16]. Other immune receptors, including toll-like receptors (TLRs), which take part in microbe-derived molecular signaling, early brain development, synaptic plasticity, and neurogenesis, have been identified as schizophrenia susceptibility genes by GWAS. Both TLR2 and TLR4 were altered in the blood and brain tissue of schizophrenic patients[15].

The genes encoding for neuregulin 1 and neuregulin 3 are candidate schizophrenia genes and produce several possible proteins that influence neuronal differentiation and migration. The role of neuregulin 1 in schizophrenia is not well known, but increased neuregulin 1 signaling led to NMDA receptor hypofunction (in accordance with the glutamate hypofunction hypothesis of schizophrenia). There is no evidence of hyperexpression of neuregulin 1 itself; however, the possibility of mutations causing the production of proteins with enhanced function is still present[14]. Neuregulin 3 is a ligand for receptor tyrosine-protein kinase erbB-4 (ErbB4), and different genetic variants of the neuregulin 3 gene, especially the rs10748842 allele, are connected with higher schizophrenia risk and cognitive impairment[17]. Mutant mice with ErbB4 deletion from fast-spiking interneurons exhibited increased cortical excitability and oscillatory activity and desynchronized neurons in the cortical region, probably caused by the disruption of the proper function of inhibitory GABA circuits in interneurons. These functional changes manifested in increased locomotion, impaired social and emotional behavior and cognitive dysfunction, which are common symptoms of schizophrenia[18,19].

The gene encoding dystrobrevin-binding protein 1 (also referred to as dysbindin or DTNBP1) has been identified as a gene associated with schizophrenia; however, no specific protein coding mutations increasing the risk of schizophrenia have been identified. Decreased dysbindin expression has been found in the brains of schizophrenia patients, and dysbindin risk haplotypes have been associated with increased negative symptomatology in schizophrenia[14].

The gene most closely linked to schizophrenia is probably the gene encoding the protein disrupted in schizophrenia 1 (DISC1), which has been associated with schizophrenia mainly due to a mutation causing a translocation between exons 8 and 9. The molecular mechanism of this mutation is not known, but the shortened mutant DISC1 protein is incapable of dimerization, and it may interact with other proteins. DISC1 expression is especially high during neurodevelopment in the late fetal and early postnatal phases, during which it participates in hippocampal development; however, DISC1 expression continues into adulthood. In schizophrenia pathophysiology, not only DISC1 itself but also its binding and interaction partners, such as microtubule-associated protein 1A, glycogen synthase kinase 3β, phosphodiesterase 4 and fasciculation and elongation protein zeta-1, might play a crucial role[14,20-22].

The synaptosomal-associated protein SNAP25 is involved in synaptic vesicle docking and fusion during neurotransmitter release. The promoter variant rs6039769 with the C risk allele caused an increase in SNAP25 expression, probably causing a larger amygdala and greater functional connectivity between the amygdala and ventromedial prefrontal cortex in male schizophrenic patients. This modulation in the plasticity of the prefrontal cortex-limbic connection caused higher schizophrenia risk [23].

The gene encoding transcription factor 4 (TCF4) is another GWAS-confirmed gene associated with schizophrenia. It encodes class I basic helix-loop-helix transcription factors and plays a role in neurodevelopment. Altered expression of TCF4 in the forebrain of a transgenic mouse caused altered cognition and long-term depression increased the density of immature spines[24]. Many other genes have been associated with schizophrenia diagnosis and have been reported in the literature[25-27]; description of all schizophrenia-linked genes is beyond the scope of this review.

TRIGGERS AND RISK FACTORS

Environmental model of schizophrenia

The onset and severity of schizophrenia are always modulated by an interplay between genetic and environmental risk factors[28]. Many epidemiological studies have investigated putative environmental risk factors for schizophrenia and peripheral biomarkers of the disease[29,30]. According to an umbrella review of meta-analyses on risk factors and peripheral biomarkers for schizophrenia[31], history of obstetric complications, exposure to stressful events in adulthood or to childhood adversity, cannabis use, and serum folate level showed robust evidence of association with schizophrenia.

The prenatal and perinatal periods are characterized by great neural vulnerability to environmental insults. A recent systematic review and meta-analysis of 152 studies revealed numerous prenatal and perinatal risk factors, calculated with odds ratios (ORs), that were statistically linked to schizophrenia onset[32]. The biggest risk factors for schizophrenia onset are any familial psychopathology, especially maternal psychosis (OR: 7.61). Maternal infections (herpes simplex 2, OR: 1.35; unspecified infections, OR: 1.27), a suboptimal number of antenatal care visits (OR: 1.83), or maternal stress (OR: 2.4) can lead to a higher prevalence of obstetric events (OR: 1.52), which are the longest-studied and best replicated environmental risk factors for schizophrenia. Significantly relevant obstetric events include maternal hypertension (OR: 1.4), hypoxia (OR: 1.63), premature rupture of membranes (OR: 2.29) and polyhydramniosis (OR: 3.05). There is experimental and clinical evidence showing significant risks of prenatal infection and inflammation for the later development of schizophrenia. According to the viral model of schizophrenia, prenatal viral and bacterial infections and inflammation play an important role in the development of schizophrenia[33].

Nutritional deficits or famine in pregnancy (OR: 1.4) or more than two pregnancies (OR: 1.3) can be associated with reduced allocation or lower socioeconomic status. Another risk factor is congenital malformations (OR: 2.35)[32]. The most relevant postnatal environmental risk factors are childhood trauma (OR: 2.87), urban living (OR: 2.19), migration (2.10) and cannabis use (OR: 5.17), and these stress factors lead to the sensitization of the subcortical dopamine system[11].

Many genes relevant to schizophrenia, especially immune genes, can be altered by air pollution. Children with greater exposure to traffic-related air pollution had increased levels of proinflammatory cytokines. It is not yet clear whether air pollution itself causes brain changes or inflammatory changes caused by air pollution contribute to the pathology of schizophrenia[15].

A study of the roles of both genetic and environmental influences on the development of schizophrenia is necessary to explain the fact that in approximately 40%-55% of cases, monozygotic twins do not share a diagnosis of schizophrenia[34]. How genetic and environmental factors interact and the related neurobiological mechanisms that induce schizophrenia are not yet known.

Stress and schizophrenia

The vulnerability-stress model of schizophrenia proposes that when stress exceeds the vulnerability threshold, an individual is likely to develop a psychotic episode[35]. Stressful life events or psychological stress, especially in key periods of neurodevelopment, increase the risk of schizophrenia. These events include physical or mental abuse, lower socioeconomic status, urban environment, and neglect. The molecular mechanisms connecting these stressful situations with schizophrenia remain unclear. It was proven that patients with schizophrenia have altered cortisol function, and its release is linked to the inflammatory response rather than the anti-inflammatory response. Observation of HPA axis activation and cortisol release as a result of stress events in individuals with schizophrenia has produced inconsistent results; however, HPA axis dysfunction has been observed[15].

Neurons are extremely sensitive to redox imbalance during neurodevelopment and differentiation, mostly because of their high lipid content and metabolic rate. Increased reactive oxygen species (ROS) production and/or lowered antioxidant system capacity are considered risk factors for schizophrenia development. Increased protein and lipid oxidation and lowered levels of vitamin C and E, catalase, glutathione peroxidase and superoxide dismutase have been detected in schizophrenia patients. A study revealed that participants with low vitamin D3 Levels in the first year of life were at two times higher risk of schizophrenia. Glutamate-cysteine ligase is the rate-limiting biosynthetic enzyme of glutathione. One allelic variant of the GCLC gene is linked to the decreased

activity of glutamate-cysteine ligase and schizophrenia. NMDA receptors are regulated by the redox state, and glutathione deficiency induces NMDA receptor hypofunction, which leads to cortical oxidative stress and glutathione decrease[36,37].

Neurodevelopmental model

The neurodevelopmental model postulates that an increased risk of schizophrenia development is the result of abnormal brain neurodevelopment caused by genetic and environmental factors years before the onset of the disease[38]. The hypothesis is based on clinical, epidemiological, brain imaging, and genetic studies[39,40]. Schizophrenia is supposed to be a developmental disorder of the brain, and changes in brain neuroplasticity are involved. The disconnection hypothesis[41] presumes the involvement of abnormal synaptic connections in the pathophysiology of schizophrenia. Impaired synaptic plasticity and synaptic efficacy, mainly in areas of the brain responsible for learning, memory, and emotion, participate in schizophrenia pathophysiology. Modulation of ascending neurotransmitter systems and consolidation of synaptic connections during learning are implicated in schizophrenia neuropsychology, especially in impaired adaptive behavior and disintegrative aspects [42].

The unitary hypothesis of schizophrenia includes different types of pathophysiological models[43]; according to the hypothesis, early brain insults can lead to dysplasia of selective neural circuits, which is responsible for premorbid cognitive and psychosocial dysfunction in patients with schizophrenia. The onset of psychosis in adolescence may be associated with the excessive elimination of synapses with subsequent dopaminergic over activity. Decreased glutamatergic neurotransmission can predispose the brain to these processes. After the onset of the disease, these neurochemical changes can lead to further neurodegenerative processes. Brain plasticity includes both synaptic and nonsynaptic plasticity. The dysplastic model of schizophrenia suggests that impaired neuroplasticity during brain development may underlie cognitive and deficit symptoms and may lead to reorganization in other neuronal circuits, which may lead to affective and psychotic symptoms[44].

The multiple hit theory of schizophrenia[45] presumes that schizophrenia can be conceptualized as a process involving multiple vulnerability factors across numerous neurodevelopmental windows in which some hits are applied prenatally, in childhood, in adolescence, and in adulthood. Thus, the development of schizophrenia is driven by the interactions between genetic vulnerability and environmental influences (including prenatal vitamin D, nutrition, childhood trauma, viral infections, IQ, smoking, cannabis use, and social defeat), which are cumulative and interact with each other. The neurodevelopmental phase involves changes in synaptogenesis, synaptic enhancement, and myelination, leading to excessive elimination of synapses and loss of neuroplasticity.

An extension of the neurodevelopmental model[46] proposes that the abnormal formation and maturation of connectomes (an extensive network of interconnected neurons) is central to the etiology of the disease. That is, abnormal anatomical architecture and functional organization of the connectome may be a final common pathway leading to the manifestation of schizophrenia symptoms. To further refine the developmental hypothesis of schizophrenia, progress in our understanding of brain connectivity during development and dysconnectivity resulting from genetic and environmental factors is necessary.

Oxidative stress and apoptosis

Disconnection of the prefrontal cortex in schizophrenic patients is associated with abnormalities in white matter, oligodendrocytes, and myelin. Myelin is produced by mature oligodendrocytes, and oligodendrocyte precursor cells are extremely sensitive to oxidative stress. A redox-induced prefrontal oligodendrocyte precursor cell-dysfunctioning hypothesis of cognitive symptomatology in schizophrenia has been proposed[47]. According to this hypothesis, the combination of environmental factors and genetic predisposition causes oxidative stress due to the excessive generation of ROS and reactive nitrogen species in oligodendrocyte precursor cells. Oxidative stress can lead to the downregulation of myelin-related genes in oligodendrocytes, decreased expression of myelin basic protein, and a reduced number of oligodendrocytes in the rat brain. During adolescence, a high concentration of ROS impairs the proliferation and differentiation of oligodendrocytes and their precursors. This leads to their dysfunction and hypomyelination and consequently to the disruption of connectivity in the prefrontal cortex. The resulting cognitive symptoms coincide with the onset of schizophrenia.

Additionally, oxidative stress induces dysregulation of the immune system and favors a proinflammatory response. Inflammation and disruption of immunity are other factors contributing to the pathogenesis of schizophrenia, as described in the following sections.

Mitochondria play a major role in cellular bioenergetics, oxidative stress, and apoptosis. According to the mitochondrial hypothesis of schizophrenia, mitochondrial dysfunction leads to distorted neuronal activity and plasticity, causing imbalanced brain circuitry and finally abnormal behavior[48]. Massive loss of white matter oligodendrocytes is a hallmark of schizophrenia. Therefore, it has been hypothesized that mitophagy is increased in oligodendrocytes in schizophrenia, which contributes to disease-related white matter neuropathology.

The intrinsic pathway of apoptosis is activated by intracellular signals generated during cellular stress and is triggered by the release of proapoptotic factors from mitochondria. Thus, consistent with the mitochondrial hypothesis, the apoptotic hypothesis postulates that apoptosis contributes to the pathophysiology of schizophrenia. The data indicate a dysregulation of apoptosis in several cortical areas in schizophrenia. The potential involvement of nonlethal localized apoptosis in the early stages of the disease is presumed[49].

NEUROCHEMICAL HYPOTHESES

Dopamine hypotheses

According to the classic (receptor) dopamine hypothesis of schizophrenia, psychotic symptoms are related to dopaminergic hyperactivity in the brain. Hyperactivity of dopaminergic systems during schizophrenia is the result of increased sensitivity and density of dopamine 2 (D_2) receptors. This increased activity can be localized in specific brain regions[50,51]. The dopamine hypothesis does not assume that dopamine hyperactivity fully explains schizophrenia. Over activation of D_2 receptors appears to be only one effect of the overall dysregulation of chemical synapses in this disease.

The modified dopamine hypothesis assumes that schizophrenia is characterized by abnormally low prefrontal dopamine activity (causing negative symptoms) that leads to excessive dopamine activity in mesolimbic dopamine neurons (causing positive symptoms). Thus, this hypothesis presumes the co-occurrence of high and low dopamine activity in different neuronal circuits, which could explain the concurrent presence of positive and negative symptoms[52].

The unifying dopamine hypothesis of schizophrenia, called "the final common pathway", proposes that multiple environmental, genetic, and other risk factors (such as stress, drugs, or frontotemporal dysfunction) interact and result in striatal dopamine dysregulation, which alters signal transmission and leads to psychosis[53]. This hypothesis combines dopamine dysfunction with other risk factors, including pregnancy and obstetric complications, stress and trauma, drug abuse, genetic predisposition and environment–gene interactions, with both increased presynaptic striatal dopaminergic function and other brain functions that underlie negative and cognitive symptoms.

A model has been presented of how genes and environmental factors may sensitize the dopamine system so that it is vulnerable to acute stress, leading to progressive dysregulation and the onset of psychosis[13]. The main steps of this model are as follows: genetic risk factors lead to impaired glutamatergic regulation, followed by increased striatal dopamine release, aberrant salience, and psychotic symptoms. Acute psychosocial stress can activate increased striatal dopamine release both directly and indirectly *via* blunted cortical dopamine release and impaired glutamatergic regulation. The dopaminergic system interacts also with muscarinic cholinergic system and closely related muscarinic hypothesis of schizophrenia.

Glutamate hypotheses

The glutamate hypothesis assumes that schizophrenia is caused by developmental abnormalities in glutamate synapse formation at specific sites, particularly at GABA interneurons in the cerebral cortex. These abnormalities may lead to subsequent excessive glutamate signaling to the ventral tegmental area (VTA), and excessive activation of this pathway may result in an excess of dopamine in the ventral striatum *via* the mesolimbic pathway[54]. The role of dysregulation of glutamatergic neurotrans-mission in the pathophysiology of schizophrenia is supported by evidence from genetics, pharmacological, postmortem, and brain imaging studies[55]. The conver-

gence of GABA impairment and glutamate neurotransmission in the dorsolateral prefrontal cortex could explain the impairment of certain cognitive functions in schizophrenia[56].

The NMDA receptor hypofunction hypothesis[57] assumes that genetic and other risk factors induce epigenetic alterations leading to NMDA receptor hypofunction in schizophrenia. NMDA receptor hypofunction induces a cascade of downstream disturbances in neuronal activity, calcium entry, and epigenetic machinery, leading to abnormal synaptic development and dopaminergic and GABAergic dysfunction. These changes in neurotransmission result in the cognitive and social deficits found in schizophrenia. According to this hypothesis, changes in the dopamine system are secondary to NMDA receptor hypofunction.

Antagonists of NMDA receptors (*e.g.*, phencyclidine) have been shown to cause symptoms similar to the positive and negative symptoms and cognitive defects in schizophrenia[58]. According to increasing evidence, deficits in NMDA transmission are linked to cognitive defects and negative symptomatology[59].

Serotonin hypothesis

There are 3 interconnected pathways hypothetically associated with hallucinations and delusions: (1) Dopamine hyperactivity at D_2 dopamine receptors in the mesolimbic pathway, which extends from the VTA to the ventral striatum; (2) NMDA receptor hypoactivity on GABAergic interneurons in the prefrontal cortex; and (3) Serotonin (5-HT) hyperactivity of 5-HT_{2A} receptors on glutamate neurons in the cerebral cortex. All 3 pathways can lead to hyperactivity of the mesolimbic dopamine pathway[54].

According to the serotonin hypothesis[60], the basic cause of schizophrenia is stress-induced serotonergic hyperfunction in the cerebral cortex, especially in the anterior cingulate cortex and the dorsolateral frontal lobe. The serotonin hypothesis assumes hyperfunction of 5-HT_{2A} receptors on glutamate neurons in the cerebral cortex. This overactivation of 5-HT_{2A} receptors may be due to an excess of serotonin, upregulation of 5-HT_{2A} receptors, or the effects of 5-HT_{2A} receptor agonists. Subsequent release of glutamate in the VTA may activate the mesolimbic pathway, resulting in excess dopamine in the ventral striatum[54].

Cannabinoid hypothesis

According to the cannabinoid hypothesis[61-63], changes in the endocannabinoid system may contribute to the pathogenesis of schizophrenia. This hypothesis proposes that increased activation of the endocannabinoid system through CB_1 receptors on GABAergic interneurons in the ventral tegmental area, basolateral amygdala, and medial prefrontal cortex may lead to a hyperdopaminergic and hypoglutamatergic status, which may cause schizophrenia. The hypothesis was supported by evidence that cannabis use in adolescence is an independent risk factor for schizophrenia development (OR: 3.90)[31] and by the confirmation of interactions between the cannabinoid and dopamine systems that may be related to the processes associated with drug addiction or schizophrenia[64].

BLOOD BRAIN BARRIER

The pathophysiology of many central nervous system (CNS) disorders, including schizophrenia, includes altered function of the blood brain barrier (BBB), as shown by evidence from neuroimaging studies, research of both cerebrospinal fluid (CSF) and blood-based biomarkers, and postmortem studies[65]. It remains to be elucidated whether BBB dysfunction is the cause or consequence of schizophrenia pathology[65]. P-glycoprotein is highly expressed in capillary endothelial cells. P-glycoprotein limits the accumulation of psychotropic drugs in the brain and is responsible for the efflux of drugs from the CNS by using the energy from ATP hydrolysis to return the compound to the bloodstream.

According to increasing evidence, malfunction of the BBB and microvascular abnormalities contribute to the pathophysiology of schizophrenia[66]. In a postmortem study, the cellular expression of ABCB1 [the gene encoding P-glycoprotein 1 (P-gp); multidrug resistance protein 1] was examined in patients with schizophrenia. A reduced density of P-gp-expressing neurons was found in the medial habenula of patients with schizophrenia compared to that of controls[66]. Furthermore, polymorphisms of *ABCB1* have been associated with changes in drug disposition and pharmacotherapy response[67].

P-gp is not the only efflux protein; multiple drug resistance (MRP) and breast cancer resistance protein (BCRP) also facilitate the efflux of ATP-dependent substrates. In addition to P-gp, BCRP (ABCG2) and the multidrug resistance proteins MRP1 (ABCC1) and MRP2 (ABCC2) are ATP-dependent efflux transporters present in the BBB[68].

Claudin-5 is a component of tight junctions and is specifically expressed in endothelial cells in the CNS. Polymorphism of claudin-5 has been associated with schizophrenia risk[65], and serum claudin-5 Levels were decreased in patients with schizophrenia[69]. The expression of claudin-5 in the hippocampus was reduced in patients with schizophrenia; the levels of claudin-5 correlated with the duration and age of onset of the disease[70]. The BBB impedes the transfer of many drugs, including antipsychotics, as well as some inflammatory molecules, such as cytokines, which play an important role in the pathophysiology of schizophrenia (see below).

Other explanations of pharmacoresistance in schizophrenia involve abnormal structure of the BBB, downregulation of genes encoding ion transport proteins, impaired immune system, dysfunctional glutamatergic transmission, *etc.*

NEUROINFLAMMATION

Based on the observation that schizophrenia is often associated with chronic neuroinflammation in the CNS[71], the vulnerability-stress model has been expanded into the vulnerability-stress-inflammation model[72], which suggests that the symptoms of schizophrenia are associated with specific changes in dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission following neuroinflammation and microglial activation. The hypothesis is based on the following findings: (1) Stress can increase proinflammatory cytokines and may even contribute to a chronic proinflammatory condition; (2) The typical changes in neurotransmission observed in schizophrenia have also been found in low-level neuroinflammation; (3) Risk factors for schizophrenia include genes whose expression promotes inflammation, environmental stressors, alterations of the immune system, severe infections, and autoimmune disorders; and (4) Antipsychotics also provide anti-inflammatory and immunomodulatory effects.

The vulnerability-stress-inflammation model of schizophrenia suggests that genetic vulnerability and infection during pregnancy may induce a proinflammatory response in the mother, causing deleterious effects on the neurodevelopment of the fetus and increasing the risk of developing schizophrenia. The development of the glutamate system may be disrupted. Re-exposure to stress at a later age may be followed by increased cytokine release, astrocyte activation or loss, dopaminergic hyperactivity, and NMDA antagonism, leading to the positive, negative, and cognitive symptoms of schizophrenia. Immune conditioning and immune sensitization can elicit a repeated response to stress leading to the symptoms of the disease.

Immunologic processes in schizophrenia

Currently, the immune system, immunological processes and inflammation are believed to have a significant role in the neurobiology of schizophrenia[73]. Evidence of immune etiology in schizophrenia comes from GWAS, where a significant association between schizophrenia and the expression of MHC, located on chromosome 6, was observed[16,74].

The relationship between neurotransmitters and mediators of the inflammatory response can be reciprocal; an immunoregulatory function of dopamine has been described. Increased expression of dopamine D_3 receptors and increased synthesis of interferon gamma (IFNγ) in lymphocytes were observed in nonmedicated patients suffering from schizophrenia[75]. An important finding from PET studies of inflammation with elevation of proinflammatory cytokines produced by microglia was an elevated microglial activity in subjects with subclinical symptoms and patients with schizophrenia[64].

Numerous studies have found immune dysregulation in patients with schizophrenia compared to healthy controls, and several meta-analyses have concluded that patients with schizophrenia exhibit signs of low-grade peripheral inflammation characterized by upregulated proinflammatory cytokines and acute phase proteins[76-78]. A recent meta-analysis of postmortem brain studies evaluating histological alterations of cellular composition and those assessing molecular parameters strengthened the immunologic hypothesis of schizophrenia[79]. The authors found significant increases in the density of microglia (especially in the temporal cortex) and

the overall expression of pro-inflammatory genes but no difference in the expression of anti-inflammatory genes in patients with schizophrenia compared to those in controls. However, it is important to note that these immunological alterations have been found only in a subgroup of patients with schizophrenia: approximately 40% of studied patients have exhibited some level of inflammation[80,81]. As schizophrenia is seen as a syndrome consisting of several disease phenotypes with different underlying pathologies, it is crucial to define robust immune biomarkers that would help in the identification of patient groups that might benefit from anti-inflammatory therapy[76, 82]. Cytokines represent a broad category of signaling molecules produced by a wide range of cells, including immune cells such as B and T lymphocytes, macrophages, and mastocytes, as well as endothelial cells and fibroblasts. A meta-analysis of 18 studies found alterations in both proinflammatory and anti-inflammatory cytokines, and these disturbances were stage dependent[83]. In patients with first-episode psychosis, elevated levels of proinflammatory cytokines were found, whereas the level of interleukin (IL)-4 was significantly reduced. In acutely ill patients, increased pro-inflammatory cytokines were observed, and lower levels of IL-4 and IL-10 Levels were found than in controls. In chronically ill patients, augmented levels of IL-1β, sIL-2R, IL-6, and tumor necrosis factor alpha (TNF-α) and reduced IFNγ levels were observed compared to those in controls. Details are summarized in Table 1.

Moreover, a study evaluating the gene expression of cytokines in peripheral blood mononuclear cells reported increased mRNA levels of IL-6, IL-8 and TNF-α and decreased anti-inflammatory IL-2 mRNA[81]. Alterations in these cytokines were also found in CFS[84], and a meta-analysis of 16 studies found significantly higher CSF levels of IL-1β, IL-6 and IL-8 in patients with schizophrenia compared to healthy controls. Interleukins (*e.g.*, IL-1β and IL-6) play important roles in neurotransmitter systems in schizophrenia. A relationship exists between increased concentrations of IL-6 in childhood and a higher risk of subclinical psychotic symptoms in young adulthood. Increased concentrations of IL-6 and other proinflammatory cytokines, such as TNF-α, IL-1β, and IFNγ, are normalized in episodes of remission after antipsychotic treatment. Some studies have suggested an association among increased serum concentrations of cytokines, including IL-6, severity of the disease, and duration and antipsychotic therapy[74].

Alterations in the immune system influence the neurotransmission of dopamine, 5-HT, norepinephrine, and glutamate. The immune system can activate indoleamine 2,3-dioxygenase, an enzyme involved in tryptophan/kynurenine metabolism[73]. Kynurenic acid acts as a naturally occurring NMDA antagonist in the human brain. Increased levels of kynurenic acid were found in the CSF of patients with schizophrenia[85,86]; however, no changes in kynurenic acid levels were observed in the peripheral blood of patients with schizophrenia[73]. Proinflammatory cytokines increase the concentration of kynurenic acid. Approximately 10% of nonmedicated patients in acute episodes of schizophrenia produce NMDA receptor antibodies, and this finding supports the hypothesis of NMDA receptor antagonism in schizophrenia [72,73].

C-reactive protein (CRP) appears to be the most promising theranostic marker for inflammation, and patients with increased CRP might benefit from anti-inflammatory therapy[76,87]. CRP is synthesized in the liver in response to IL-1β, IL-6 and TNF-α and is released from macrophages and adipocytes[76]. CRP has been reported to correlate both with positive and negative symptoms of schizophrenia[88] and with cognitive dysfunction[89]. Recently, "ultraresistance" to treatment in schizophrenia (defined as current clozapine treatment and a mean positive and negative syndrome scale (PANSS) score ≥ 70) was found to be associated with abnormal CRP levels (> 3 g/L), providing further justification for treating ultra-resistant patients with anti-inflammatory agents[90]. Additionally, other acute phase proteins, including haptoglobin, alpha-1 antitrypsin, and alpha-2-macroglobulin, were also found to be elevated in a subgroup of individuals with schizophrenia and other psychoses[91,92].

Additional biomolecules and metabolites essential for inflammation and endothelial cell function (*e.g.*, creatine kinase m/B, angiotensin-converting enzyme, matrix metalloproteinase, thyroid-stimulating hormone, thyroxine-binding globulin, intercellular adhesion molecule 1, cortisol, α-2-macroglobulin, and thrombopoietin) have been found in lower concentrations in drug-naïve patients than in controls[93]. The authors commented that most of these proteins are involved. Additionally, upregulation of leucocyte adhesion molecules was described in psychotic disorders, increased levels of soluble L-selectin were detected in the serum of drug-naïve patients with schizophrenia, and the serum levels of L-selectin and P-selectin in patients with schizophrenia did not differ from those in healthy controls[94]. In another study, P-selectin plasma levels were found to be increased in patients with acute psychosis[95].

Table 1 Possible diagnostic/theranostic immunologic biomarkers in schizophrenia

Parameter	Serum/plasma/peripheral blood	CSF
Pro-inflammatory cytokines	↑ IL-6, IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-12, sIL-2R, TGF-β, and TNF-α	↑ IL-1β, IL-6 and IL-8
Anti-inflammatory cytokines	↓ IL-10 and IL-4	
Acute phase proteins	↑ CRP, haptoglobin, α-1 antitrypsin, and α-2 macroglobulin	
Antibodies	↑ Anti-cardiolipin IgG and anti-NMDA receptor titers	
Immune cells	↑ CD4+, CD3+ and CD56+	
Other biomolecules/metabolites	↓ Creatine kinase m/B, MMP3, ACE, cortisol, TBG, α-2 macroblobulin, thrombopoietin, TSH, and ICAM-1, P-selectin	

ACE: Angiotensin-converting enzyme; CRP: C-reactive protein; CSF: Cerebro-spinal fluid; ICAM: Intercellular adhesion molecule; IFNγ: Interferon gamma; IL: Interleukin; MMP3: Matrix metalloproteinase 3; NMDA: N-methyl-D-aspartate; TBG: Thyroxine-binding globulin; TGF-β: Transforming growth factor-beta; TNF-α: Tumor necrosis factor-alpha; TSH: Thyroid-stimulating hormone.

Certain studies have also found changes in the number of immune cells in patients with schizophrenia compared to healthy controls. A meta-analysis of 16 studies evaluating blood lymphocyte counts found a significant increase in the percentages of CD4+ (T-helper lymphocytes) and CD56+ (natural killer cells) lymphocytes in acutely relapsed inpatients and a significant increase in the absolute numbers of total lymphocytes and CD3+ (T-lymphocytes) and CD4+ cells[96]. However, a significant decrease in the percentage of CD3+ cells was found in drug-naïve patients in the first episode of schizophrenia. Additionally, some autoimmune responses were also found in schizophrenic patients, but their clinical relevance remains elusive. Regarding the pathogenesis of schizophrenia, different autoantibodies, as well as antibodies against diet antigens, *e.g.*, gliadin and casein, were investigated in different parts of the brain, serum, and CSF. A systematic quantitative review of 81 studies found significantly increased anti-cardiolipin IgG and anti-NMDA receptor autoantibody titers in patients in the first episode of schizophrenia[97]. The authors also reported increased titers of anti-cardiolipin IgG and IgM and nerve growth factor in patients with schizophrenia compared with controls.

As mentioned, there is a strong link between oxidative stress and the immune system; therefore, by counteracting oxidative stress, antioxidants reduce inflammation and the overactive immune response. Glutathione is an antioxidant that is essential in the myelinization and maturation of white matter and can be supplemented as the amino acid precursor N-acetyl cysteine. N-acetyl cysteine possesses antioxidant properties and mild anti-inflammatory effects and regulates synaptic NMDA receptors. NAC supplementation for 6 mo ameliorated positive symptoms and improved neurocognition (processing speed) in patients with schizophrenia with high peripheral oxidative stress[98]. Omega-3-type polyunsaturated fatty acids have also exerted antioxidative capacity and anti-inflammatory effects[99].

Non-steroidal anti-inflammatory drugs in pharmacotherapy

Anti-inflammatory agents have shown some benefits as adds-ons to antipsychotic treatment in schizophrenia, as reported by two recent meta-analyses[100,101]. A meta-analysis of 62 double-blind randomized clinical trials studying aspirin, celecoxib, omega-3 fatty acids, estrogens, pregnenolone, minocycline, N-acetyl cysteine, and erythropoietin in 2914 patients found an overall significant effect of a decrease in the PANSS score[100]. Additionally, cognitive improvement was significantly associated with minocycline and pregnenolone therapy. Another meta-analysis of 70 randomized clinical trials including 4104 subjects investigated either primarily non-steroidal anti-inflammatory drugs (NSAIDs), minocycline and monoclonal antibodies, or drugs with potential anti-inflammatory properties (N-acetyl cysteine, melatonin, neurosteroids, estrogens, fatty acids, statins, and glitazones) as adjunctive therapies to antipsychotics. The analysis also found a decrease in the PANSS score[101]. Small but significant effect sizes were observed on both negative and positive symptoms, general psychopathology and working memory. Interestingly, primarily anti-inflammatory drugs were not found to be superior to potential anti-inflammatory drugs. However, the authors highlighted that the reported effects might be overestimated due to the many small study samples included in the analysis.

In conclusion, changes in the frequencies of immune cells, the levels and expression of cytokines, and the levels of acute phase proteins in the blood and CSF were observed in patients with schizophrenia compared to healthy controls, and CRP seems to be a promising theranostic biomarker for schizophrenia. Moreover, larger studies with longer treatment durations and the inclusion of only schizophrenic patients with proven inflammation (CRP levels > 3 g/L) are warranted to elucidate the efficacy of anti-inflammatory treatment in schizophrenia.

The challenges of drug development include the development of novel molecules affecting the immune system and of immunotherapy using autoantibodies as well as the stratification of patients with schizophrenia according to their immune phenotypes to enable the selection of effective pharmacotherapeutic agents[74].

MICROBIOME-BRAIN AXIS MODEL

The microbiome-gut-brain axis model postulates that bidirectional communication between the central and enteric nervous systems ensures the connection of the brain with peripheral intestinal functions[102,103]. It is presumed that the gut microbiome can program brain function during early development; in other words, active signals from the microbiome play a critical role in brain development. It is thought that the microbiome may affect brain development through epigenetic mechanisms[104]. Signal pathways from the gut microbiome to the brain include: (1) The direct activation of the vagus nerve; (2) The production or induction of various metabolites that may cross the BBB to regulate neurological functions; and (3) An immune system whose cytokines affect neurophysiology[105].

Probiotics modulate the immune responses of the host and could be beneficial for schizophrenia patients[106]. The immunomodulatory effects of probiotic supplementation were examined after 14 wk in chronic patients with schizophrenia, and *Lactobacillus* and *Bifidobacterium* were administered as adjuvant treatments. Increased levels of brain-derived neurotrophic factor, chemokine ligand 5 (RANTES), monocyte chemotactic protein and macrophage inflammatory protein-1 beta were found[106]. Gut-brain communication suggests the direct secretion of some neuroactive substances, and some intestinal bacteria can produce mediators, *e.g.*, GABA, acetylcholine.

INNOVATIVE DRUG APPROACHES AND TARGETS

All antipsychotics for schizophrenia treatment are based on dopamine agonism/antagonism, and no nondopaminergic antipsychotics have yet been developed or approved (Figure 1). Lumateperone is characterized as a partial D_2 receptor agonist/antagonist and a 5-HT_{2A} antagonist, and it is a serotonin reuptake inhibitor that indirectly modulates glutamatergic transmission (effect on NMDA receptor subtype 2B, NR2B)[107,108]. It has no metabolic or extrapyramidal adverse effects and positively affects cognition[109]. Another study found that lumateperone was well tolerated with minimal extrapyramidal and cardiometabolic adverse effects and maintained or reduced the symptoms of schizophrenia after a switch from a previous antipsychotic[110].

A promising therapeutic drug strategy for schizophrenia is the use of antipsychotics without D_2 receptor binding[111]. Agonists of trace amine-associated receptor 1 (TAAR1) seem to selectively affect dopamine and may represent a new class of psychotropic drugs[112,113]. A novel compound, SEP-363856, was described as a TAAR1 and 5-TH_{1A} agonist and was tested in a pilot trial with 120 patients with an acute exacerbation of schizophrenia. The reduction in the PANSS score of the treatment group was significant compared with that of the placebo group; longer and larger trials are necessary to prove the efficacy and safety of this TAAR1 agonist[113]. Other TAAR1 agonists, *e.g.*, RO5263397, have been developed and are being tested for use in schizophrenia. RO5263397 was found to be safe, but a great variety in metabolism and plasma levels was found that depended on ethnicity and genotype [112,114].

Novel drugs indirectly targeting glutamate neurotransmission are among the strategies being pursued for antipsychotic development. Inhibitors of glycine transporters (*e.g.*, sarcosine and bitopertin), coadministration of NMDA agonists, allosteric modulators of AMPA receptors (ampakines), and allosteric modulators of $mGluR_5$ are being tested; novel drugs affecting the glutamate ionotropic and meta-

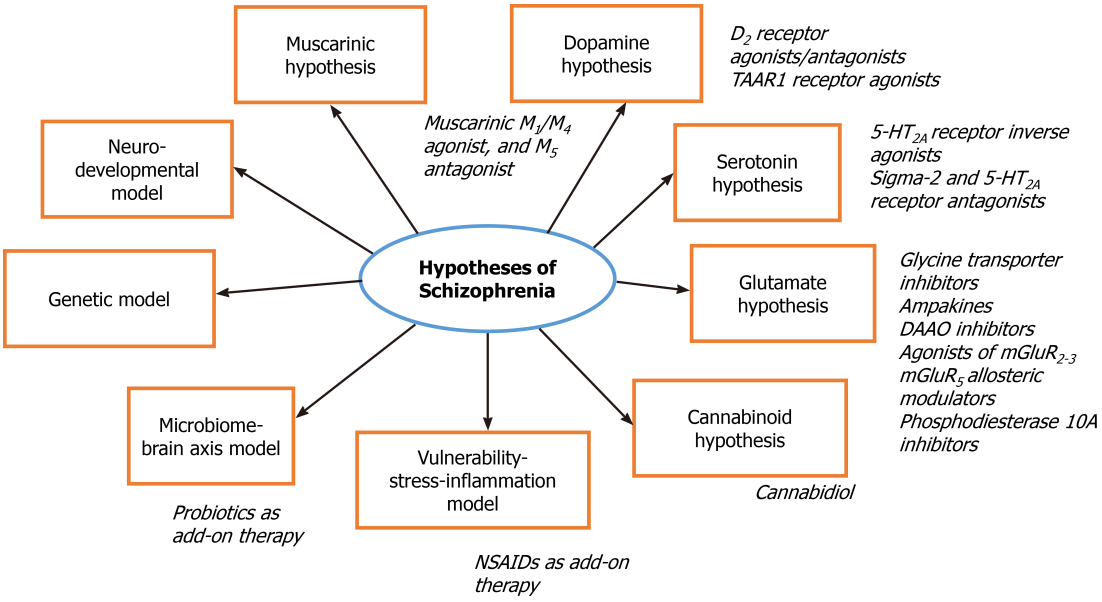


Figure 1 Illustration of current hypotheses and novel approaches in treatment of schizophrenia. DAAO: D-Amino acid oxidase; TAAR1: Trace amine-associated receptor 1; NSAIDs: Non-steroidal anti-inflammatory drugs.

botropic receptors $mGluR_{2-3}$ have been developed[115].

Agonists of $mGluR_{2-3}$ have anxiolytic properties and reverse the effects of stress; agonists of the $mGluR_3$ receptor antagonize the effect of phencyclidine and amphetamine. Novel drugs directly affecting receptors were found to be ineffective and/or to have adverse effects. Pomaglumetad methionil is an $mGluR_{2-3}$ agonist[58]. It was tested as an adjunctive therapy for patients with negative symptoms of schizophrenia, and the study did not find a difference between the pomaglumetad group and the placebo group[116]. Post hoc analyses suggested the efficacy of pomaglumetad in patients suffering from schizophrenia for less than or equal to 3 years or in patients previously treated with antipsychotics predominantly acting as D_2 antagonists [117,118]. Thus, the potential of novel $mGluR_{2-3}$ agonists is suggested for treating psychosis and aggression/agitation associated with neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, dementia with Lewy bodies, *etc.*)[117].

D-Amino acid oxidase (DAAO) inhibitors were found to modulate NMDA transmission. Sodium benzoate, a DAAO inhibitor, has been tested as an add-on therapy and improved symptoms in clozapine-resistant patients[119]. In another study, sodium benzoate was administered to patients with schizophrenia as an add-on therapy compared to placebo. The adjunctive therapy was well tolerated, and chronic schizophrenia patients showed improved function, especially neurocognition[120].

Cannabidiol seems to be a promising candidate for the treatment of schizophrenia. Increased function of the endocannabinoid system was observed in schizophrenic patients; cannabidiol was found to decrease mesolimbic dopaminergic activity. There is evidence that chronic and acute administration of cannabidiol led to improvement of schizophrenia symptomatology[121].

Based on the serotonin hypothesis, pimavanserin was developed and characterized as an inverse agonist at 5-HT_{2A} receptors, and it has binding affinity for sigma-1 receptors. This antipsychotic has been FDA-approved for the treatment of psychosis associated with Parkinson's disease. Further randomized controlled trials are needed to consider pimavanserin as a drug for schizophrenia treatment[122].

Antagonism at sigma-2 receptors was described for roluperidone, which was developed as a novel antipsychotic affecting 5-HT_{2A} receptors and sigma-2 receptors [58]. Roluperidone has been found to be effective in the treatment of negative symptoms[123].

Xanomeline is a muscarinic M_1/M_4 agonist and M_5 antagonist that was originally developed for Alzheimer´s disease. Currently, it is being tested in combination with trospium, which reduces peripheral adverse effects (nausea and vomiting), as a new antipsychotic with a novel mechanism of action.

Phosphodiesterase inhibitors have been investigated as drugs to enhance cognition in schizophrenia[124]. Phosphodiesterase 10A inhibitors likely modulate D_1 (directly) and D_2 (indirectly) striatal pathways and regulate glutamate receptors[112]. TAK-063, a

phosphodiesterase 10A inhibitor, was tested, but the clinical trial did not meet the primary endpoint, and extrapyramidal syndromes occurred more often in the TAK-063 group than in the placebo group[125].

CONCLUSION

Genetic predisposition and neurodevelopmental and environmental risk factors for schizophrenia were summarized. Nevertheless, the understanding of schizophrenia pathophysiology is limited, and current pharmacotherapy is complicated by adverse effects, pharmacoresistance, and low compliance of patients. Novel targets and approaches of antipsychotic treatment are being developed with the aim of covering the wide range of schizophrenia symptoms, especially negative symptomatology, cognitive impairment, and residual and treatment-resistant symptoms. Novel drug targets based on current schizophrenia hypotheses include molecules indirectly targeting glutamate neurotransmission, DAAO inhibitors, 5-HT_{2A} receptor inverse agonists, sigma-2 receptor antagonists, phosphodiesterase inhibitors, *etc*. In pharmacoresistant patients, possible comorbidities may be related to inflammation or a disrupted microbiome-gut-brain axis, and augmentation of antipsychotic treatment *via* NSAID or probiotic administration can be considered. Further research on schizophrenia pathophysiology, genetic predisposition (based on GWAS), regulatory mechanisms in impaired mediator transmission and other factors is needed to improve the clinical outcomes of pharmacotherapy.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 297-315

DOI: 10.5498/wjp.v11.i7.297

ISSN 2220-3206 (online)

REVIEW

Glutamate and depression: Reflecting a deepening knowledge of the gut and brain effects of a ubiquitous molecule

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Author contributions: Both authors contributed equally to the writing of this manuscript.

Conflict-of-interest statement: Authors have nothing to declare.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Nigeria

Peer-review report's scientific quality classification

Grade A (Excellent): 0

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Abstract

The versatility of glutamate as the brain's foremost excitatory neurotransmitter and modulator of neurotransmission and function is considered common knowledge. Years of research have continued to uncover glutamate's effects and roles in several neurological and neuropsychiatric disorders, including depression. It had been considered that a deeper understanding of the roles of glutamate in depression might open a new door to understanding the pathological basis of the disorder, improve the approach to patient management, and lead to the development of newer drugs that may benefit more patients. This review examines our current understanding of the roles of endogenous and exogenous sources of glutamate and the glutamatergic system in the aetiology, progression and management of depression. It also examines the relationships that link the gut-brain axis, glutamate and depression; as it emphasizes how the gut-brain axis could impact depression pathogenesis and management *via* changes in glutamate homeostasis. Finally, we consider what the likely future of glutamate-based therapies and glutamate-based therapeutic manipulations in depression are, and if with them, we are now on the final chapter of understanding the neurochemical milieu of depressive disorders.

Key Words: Brain; Gut microbiome; Mental health; Mood disorders; Neurotransmitters

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Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

Received: March 7, 2021
Peer-review started: March 7, 2021
First decision: March 30, 2021
Revised: April 13, 2021
Accepted: May 10, 2021
Article in press: May 10, 2021
Published online: July 19, 2021

P-Reviewer: Pasquini M, Pavón L, Qu SQ
S-Editor: Gao CC
L-Editor: Webster JR
P-Editor: Li JH

Core Tip: The versatility of glutamate as the brain's foremost excitatory neurotransmitter, and modulator of intermediary metabolism in the gastrointestinal tract is considered common knowledge. Years of research suggest glutamate has a role to play in depression. Also, there is increasing evidence of a possible relationship between glutamate and the pathophysiology and/or treatment of depression. The complexity of depression suggests dysregulation of glutamate in sites such as the gastrointestinal tract and brain. The communication link involving dietary glutamate, the gut, endogenous glutamate, and the brain is a multidirectional pathway; the understanding of which is necessary to fully account for glutamate's role in depression.

Citation: Onaolapo AY, Onaolapo OJ. Glutamate and depression: Reflecting a deepening knowledge of the gut and brain effects of a ubiquitous molecule. *World J Psychiatr* 2021; 11(7): 297-315
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/297.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.297

INTRODUCTION

Clinical depression or major depressive disorder (MDD) is a chronic, debilitating, and disabling mental health disorder that affects over 300 million people (across all age groups) globally[1-4]. It contributes significantly to the global burden of disease and escalating incidence of suicides amongst teenagers and young adults worldwide. Globally, the prevalence of depression continues to increase[4,5]; with factors such as worsening poverty, increasing unemployment, adverse life events and genetics[4] being recognized as important risk factors for its development.

The discovery of monoamine oxidase inhibitors and tricyclic antidepressants opened opportunities for the treatment of depression and provided insights into the role of neurotransmitters such as dopamine, serotonin and norepinephrine in the pathophysiology of depression[6,7]. However, the shortcomings of the currently-approved pharmacotherapies such as the lag time between the effect of drugs on monoamine availability and their therapeutic effect, inadequate response, and the increasing incidence of treatment-resistant depression[7-9] means that there is still a critical need to better understand the pathophysiology of depression; and develop more-effective and efficient therapeutic interventions for depressive disorders.

The monoamine hypothesis supports the notion that the pathology in depression is primarily depletion in the levels of brain monoamine neurotransmitters including serotonin, norepinephrine, and dopamine[10-12]. In the almost seven decades since its formulation, it has largely explained the symptoms and response to currently available antidepressant therapy. However, inconsistencies in the hypothesis have resulted in further research to better understand depression pathophysiology and management. In the last three decades, there has been compelling clinical[13,14] and preclinical[15,16] evidence demonstrating the involvement of the glutamatergic system in the pathophysiology of depression.

Since the first mention of the glutamate hypothesis of depression in the 1990s[15], our understanding of the versatility of glutamate as the brain's foremost excitatory neurotransmitter, and modulator of neurotransmission and function has increased considerably. Years of research have continued to uncover glutamate's effects and roles in several neurological and neuropsychiatric disorders, including depression. More recently, the antidepressant actions of ketamine, an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist especially in treatment-resistant depression [17,18] was reported; suggesting a deeper understanding of the roles of glutamate in depression could open new doors to understanding the pathological basis of the disorder, improve the approach to patient management, and lead to the development of newer drugs that may benefit more patients. Also, the roles of the gut-brain axis in glutamate signalling have been investigated, with reports that these could also impact the pathophysiology and treatment options in depression[19,20]. This review examines current understanding of the roles of endogenous and exogenous sources of glutamate and the glutamatergic system in the aetiology, progression and management of depression. It also examines the relationships that link the gut-brain axis, depression and glutamate (Figure 1); as it emphasizes how the gut-brain axis could impact

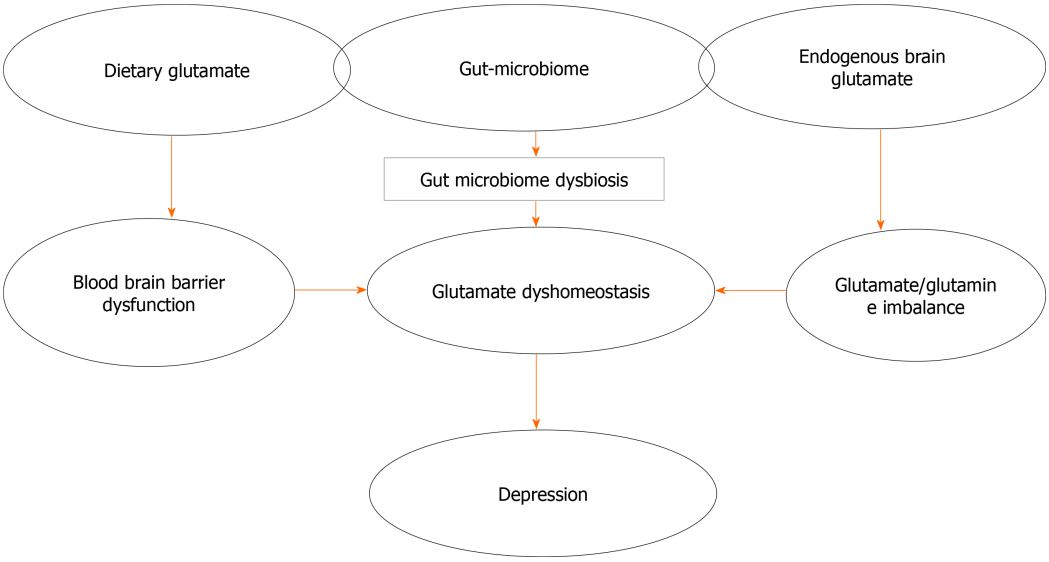


Figure 1 Possible relationships that link dietary glutamate, the gut-brain axis, endogenous glutamate and depression.

depression pathogenesis and management *via* changes in glutamate homeostasis. Finally, we consider what the likely future of glutamate-based therapies and glutamate-based therapeutic manipulations in depression are, and if with them, we are now on the final chapter of understanding the neurochemical milieu of depressive disorder.

GLUTAMATE AND DEPRESSION

Glutamate is an amino acid and the major excitatory neurotransmitter in the brain[21]. In the last few decades, there has been increasing insights into the roles played by the glutamatergic system (Figure 1) in the pathophysiology and treatment of mood disorders generally, and depressive disorders specifically[12,22,23]. Although glutamate is ubiquitous in the brain, excessive release of glutamate has been associated with excitotoxicity-induced brain injury[24]. The possible involvement of the glutamatergic system in mood disorders is supported by preclinical evidence of the antidepressant effects of NMDA antagonists[15,25]. Also, the results of early studies showing alterations in the levels of glutamate (peripherally and centrally) in persons with mood disorders confirmed this involvement[13,26]. Alterations in excitatory and/or inhibitory neurotransmitters resulting in the alteration of functional connectivity patterns within large brain networks have also been reported[27]. More recently, there is overwhelming evidence of the anxiolytic and antidepressant response to subanaesthetic-doses of ketamine in clinical[27-30] and preclinical studies[31,32].

The ability of diet to cause depression and depression-like phenotypes has been reported[33,34]. Research has continued to show that the consumption of diets rich in fat, deficient in magnesium, or high in monosodium glutamate can cause depression-like behaviours such as decreased social interaction, anhedonia and behavioural despair in rodents[35-37]. While there have been suggestions that these effects are linked to the ability of dietary factors to alter the composition of the gut microbiota[36,37], emerging evidence of the interactions between the gut microbiota and brain neurotransmitters such as dopamine, serotonin, gamma amino-butyric acid and glutamate[9,38] are opening new vistas into possible novel treatment modalities for depression.

Dietary glutamate and depression

Glutamate is an α-amino acid that is useful in the biosynthesis of proteins and important in intermediary metabolism, through its ability to link carbohydrate and amino acid metabolism *via* the tricarboxylic acid cycle[39,40]. Glutamate (in addition to being synthesized in the body in humans) is also derived from dietary sources such as cheese, meat, and several food-seasonings including monosodium glutamate[21,41].

While endogenous brain glutamate has been linked to the pathophysiology of psychiatric conditions such as schizophrenia and mood disorders, the possible role of dietary glutamate (Table 1) in the development of neuropsychiatric conditions is still being evaluated[42]. There have been suggestions that the consumption of diets containing high concentrations of monosodium glutamate could increase body levels of glutamic acid, resulting in hyperglutamatergic neurotransmission, which could possibly contribute to the development of depression[43]. Also, a few studies have reported that factors such as chronic stress that reduce brain levels of glutamate and glutamine causing hypoactive glutamatergic signaling in the mouse prefrontal cortex are also associated with the development of depression[44], suggesting that regarding brain glutamatergic transmission a delicate balance always needs to be maintained.

In the last few years, reports from preclinical studies have associated the use of monosodium glutamate with the development of behavioural phenotypes such as anxiety and depression; and the ability to influence brain endogenous glutamate and glutamatergic neurotransmission[35,42,44-46]. There have also been reports from studies that monosodium glutamate could directly influence the concentrations of brain neurotransmitters such as serotonin and glutamate[21,35,45,47], although there have also been reports to the contrary[48].

The relationship between dietary monosodium glutamate and depression has been examined by a few studies[35,43,47]. The results of a clinical analysis that examined the relationship between the consumption of a diet high in glutamic acid and the development of depressive symptoms in a group of persons with schizophrenia revealed that in non-obese patients the consumption of high dietary glutamic acid was associated with an increase in depressive symptoms, although this was linked to the susceptibility of persons with one psychiatric condition to develop other co-morbidities[42]. A preclinical study by Quines *et al*[35] that examined the effects of monosodium glutamate administered parenterally in the neonatal period with exposure to behavioural paradigms on postnatal days 60-64 reported the presence of anxiety and behavioural despair. However, studies from our laboratory revealed that while orally administered monosodium glutamate was associated with the development of anxiety behaviour, especially in male mice[21,45,49], an antidepressant effect was observed in the behavioural-despair paradigms irrespective of sex [47]. The results of these studies from our laboratory suggest that the antidepressant response observed when monosodium glutamate was administered by gavage (compared to the response following parenteral administration) could have been influenced by the gut microbiota or the gut-brain axis, or by the ability of monosodium glutamate (at these doses) to minimally increase brain levels of glutamate which could have antidepressant benefits as previously reported[44].

Endogenous brain glutamate and depression

Glutamate plays an important role in the modulation of synaptic plasticity and transmission. It is also the precursor of the inhibitory neurotransmitter gamma amino-butyric acid (GABA). Studies have shown that dysregulation of glutamatergic transmission or alterations in brain concentrations of glutamate is associated with derangement of brain function, development of excitotoxic brain injury, and cell death [24,47]. There have also been reports showing that alterations in glutamatergic neurotransmission contribute significantly to the development of peripheral and central nervous system disorders[50]. In the last few years, the possible relationships that exist between glutamate/glutamatergic system and the development of neuropsychiatric disorders such as depression have continued to be examined[22,24,51].

Several studies have linked dysregulation of glutamate neurotransmission with the development and progression of neurodevelopmental, neurodegenerative and psychiatric disorders such as autism, epilepsy and schizophrenia[52,53]. There is also emerging evidence (Table 2) linking the pathogenesis of depression to alterations in glutamate and glutamate signalling[12,52]. Levine *et al*[54], using a proton magnetic resonance spectroscopy (MRS) technique examined the relationship between cerebrospinal fluid (CSF) metabolites, such as glutamate and glutamine on depressive symptoms in hospitalized persons with severe unmedicated depression, and reported that compared to control subjects, glutamine level in the CSF of depressed patients was elevated. Also, using high performance liquid chromatography with fluorometric detection, Mitani *et al*[55] examined the relationship between plasma levels of glutamate on severity of depression and concluded that plasma levels of glutamate as well as alanine and L-serine were reflective of the severity of depression. The impact of brain glutamate levels on depression and depression phenotypes have been studied extensively[56-60]. Auer *et al*[56] and Hasler *et al*[57] using MRS reported region-specific changes in the levels of brain glutamate in patients with depression. The result

Table 1 Dietary glutamate and depression

Subject	Outcome	Ref.
Human	In non-obese participants, diets high in levels of glutamic acid were associated with greater depression symptomatology	Kumar *et al* [43]
Adult mice	While chronic immobilization stress decreased sodium-coupled neutral amino acid transporter (SNAT)-1 and 2 in neurons and glutamate transporter (GLT)1, SNAT3, and SNAT5 in astrocytes in the medial prefrontal cortex, glutamine—supplemented diet ameliorated these decrements	Baek *et al*[44]
Neonatal rats	Subcutaneous injection of monosodium glutamate (MSG) increased the immobility time in the forced swim test and the freezing reaction in the contextual fear conditioning. MSG also increased serotonin uptake in the cerebral cortices and caused deregulation of the hypothalamic-pituitary-adrenal axis	Quines *et al* [35]
Mice	Anxiolytic and memory-enhancing effects at low doses of MSG; however, at higher doses, anxiety and memory retardation were observed	Onaolapo *et al* [45]
Mice	Higher doses of dietary glutamate resulted in an increase in plasma glutamate and glutamine but no difference in total brain glutamate or glutamine levels	Onaolapo *et al* [21,45,46]
Mice	Anxiolytic response in females, and anxiogenic response in males following dietary MSG. A decrease in behavioural despair was observed in both sexes (females more than males)	Onaolapo *et al* [46,47]
Mice	Anxiogenic effect was observed following subchronic oral administration of MSG	Onaolapo *et al* [49]

Table 2 Endogenous glutamate and depression

Subject	Method	Outcome	Ref.
Human	Using a proton magnetic resonance spectroscopy technique	Compared to control subjects, glutamine levels in the cerebrospinal fluid of the depressed patients were elevated	Levine *et al* [54]
Human	High performance liquid chromatography with fluorometric detection	Plasma levels of glutamate as well as alanine and L-serine were reflective of the severity of depression	Mitani *et al* [55]
Human	Single voxel (1)H-Magnetic resonance spectroscopy in 19 patients with major depressive episodes	A significant decrease was observed in the levels of glutamate and glutamine in the anterior cingulate	Auer *et al*[56]
Human	Magnetic resonance spectroscopy	Depressed patients had reduced glutamine and glutamate levels in the dorsomedial/dorsal anterolateral prefrontal cortex	Hasler *et al* [57]
Human	Magnetic resonance spectroscopy	Compared with controls, depressed patients showed an increase in glutamine levels	Godlewska *et al*[59]
Human	Meta-analysis	Decreased levels of glutamatergic metabolites were observed in the medial frontal cortex of depressed subjects	Moriguchi *et al*[60]
Human	Meta-analysis	Glutamate and glutamine concentrations were found to be lower in the anterior cingulate cortex in patients compared to controls	Luykx *et al* [58]
Human	Functional magnetic resonance imaging and magnetic resonance spectroscopy	Patients with anhedonic major depression showed decreased glutamine but normal glutamate and gamma-aminobutyric acid concentrations	Walter *et al* [61]
Human	Resting state functional magnetic resonance imaging	Decreased amplitude of low frequency fluctuation level in right putamen and right middle temporal cortex correlated positively with glutamate concentration in female patients with depression	Zhang *et al* [66]
Mice	Preclinical study	Blockade of glutamate transporter-1 in the central amygdala and prefrontal cortex induced both anhedonia and anxiety	John *et al*[62,63]

of a recent meta-analysis of MRS studies also supported the hypothesis that glutamatergic neurotransmission was involved in the pathophysiology of depression[60]. In another meta-analysis, Luykx *et al*[58] also reported region and state specific alterations in glutamate and glutamine concentrations in depression. The importance of glutamatergic neurotransmission in depression has been further supported by studies that showed altered glutamine concentrations despite normal glutamate levels [59,61].

Abnormalities of the glutamatergic system such as those associated with glutamate clearance at the synaptic cleft and glutamate-related alterations in astrocytic energy modulation have also been observed in depression[61,62]. The results of preclinical studies have also demonstrated that blockade of astrocytic glutamate uptake in the prefrontal cortex and central nucleus of the amygdala was associated with the development of anhedonia and anxiety[62,63]. Furthermore, results from post-mortem

and magnetic resonance imaging studies have also revealed the presence of altered expression of glutamate-related genes, elevated levels of glutamate, reduced glutamine/glutamate ratio, and/or reduced levels of glutathione (a reservoir of neuronal glutamate) in brain regions such as the medial prefrontal cortex (which have been linked to depression symptomatology) in persons with depression[64-67].

Finally, the rapid antidepressant effects of drugs such as tianeptine and NMDA receptor antagonist ketamine further validate the importance of glutamate and the glutamatergic transmission in depression[22,68,69]. While reports provide some evidence for the involvement of endogenous glutamate in the pathogenesis and treatment of depression[22,50,69,70], the complexity of the disorder would suggest that the dysregulation of glutamate needs to occur in multiple sites (Figure 1) such as the gastrointestinal tract and brain, as can be seen if there is a communication link involving exogenous glutamate, the gut, endogenous glutamate, and then the brain in a multidirectional pathway which we would call the "GLUTAMATE-GUT-GLUTAMATE-BRAIN AXIS".

The gut-brain axis and glutamate

The impact of the gut (microbiota and gut peptides) in times past was not considered significant in brain development and functioning. Previously, it was believed that the commensal bacteria and their genes which constitute the gut microbiome enjoy a symbiotic relationship with man. In this relationship, they reside in a nutritionally enriched and protected habitat of the human gastrointestinal tract, while they in turn protect humans against colonization of the gut by pathogenic bacteria and provide the body with a rich source of indigestible nutrients. In the light of new evidence, it is now clear that they also play a key role in the brain, either in health or disease.

The gut-brain axis or microbiome-gut-brain axis describes the bidirectional, at times multidimensional system of communication that links the gastrointestinal tract with the central nervous system. It ensures that not only does the central nervous system modulate gastrointestinal function; the gut can also regulate or modulate brain signalling and impact brain structure and function[19]. There is now ample evidence supporting the view that the microbiome-gut-brain axis can influence the development or progression of central nervous system disorders. Some of these include observations of psychiatric co-morbidities occurring in several enteric neuropathies such as chronic inflammatory intestinal disorders[38,71,72]. The presence of altered gut microbial flora and concentration in neurodevelopmental disorders such as autism[73,74] as well as the results of microbial challenge using pathogenic bacteria or pharmacological manipulations with pre or probiotics, are also pointers to the possible roles played by the gut microbiota in the development of brain disorders[72,75]. Further reports have also shown that the gut microbiota influences brain function *via* its ability to modulate endocrine, immunologic and neurocrine signalling pathways; and brain neurotransmitters[38,76].

Also, several possible mechanisms through which microbiome-gut-brain communication could impact the genesis or progression of central nervous system disorders have been proposed. There have been suggestions that communications occur through the activation of neurotransmitters such as serotonin, dopamine, GABA and noradrenaline in the enteric nervous system; these neurotransmitters are secreted by gut microbiota and are akin to the neurotransmitters in the central nervous system [76]. The possible role of gut peptides and metabolites as mediators of the gut-brain crosstalk have also been suggested[77].

Gut-brain axis and depression

Studies have continued to demonstrate the deleterious effects that alterations in gut microbiome composition and microbiome-related metabolites could exert on the development of obesity, autoimmune disorders, inflammatory bowel disease, irritable bowel syndrome, and neuropsychiatric disorders[77-80]. Also, scientific information showing how gut microbes and gut stimuli (such as intragastric infusion of glucose or fatty acid) can directly influence emotional and cognitive functions[81,82] are pointers to the possible involvement of the gut-brain axis in psychiatric disorders. Several preclinical studies have also shown that the gut microbiota modulates brain behaviours such as behavioural despair, anhedonia and anxiety-like behaviours that have construct validity with clinical depression and anxiety[83-86]. Arentsen *et al*[84] and Kamimura *et al*[86] showed that compared to specific pathogen-free (SPF) mice, germ-free (GF) mice showed impaired social interactions choosing to spend more time with an object than conventionally raised mice. Huo *et al*[85] also observed that the exposure of GF mice and SPF mice to chronic restraint stress paradigm was associated with an increase in open field exploration time in GF compared to the SPF mice; with

SPF mice exhibiting more anxiety-like behaviours compared to GF mice. Chronic prebiotic administration has also been shown to exhibit anxiolytic and antidepressant behaviours in mice. The ability of the prebiotic to modulate behaviour correlated positively with its effects on hippocampal and hypothalamic gene expression and its ability to ensure a balance in the concentrations of short-chain fatty acids[87].

Although the mechanisms by which the gut microbiota influences mood and mood-related behaviours are still being studied; there have been suggestions that because the gut and brain share peptide and receptor similarities the gut microbiome is able to modulate brain function through the activity of gut peptides[77]. Also, studies evaluating the impact of gut microbiome modulation (using prebiotics and probiotics) on brain function have demonstrated that chronic treatment with prebiotic had both antidepressant and anxiolytic effects, which could be linked to reduction in stress-induced corticosterone and proinflammatory cytokine release, and modification of the expression of specific genes in the hippocampus[86,87]. Also, probiotics such as GABA-producing *Lactococcus lactis* strain have been shown to possess the capacity to modulate behaviours. In one study, in which *Lactococcus lactis* was grown in both glutamate and non-glutamate supplemented media, a significant increase in GABA production was observed in the glutamate supplemented medium[87], reinforcing the importance of glutamate in the modulation of mood and mood disorders.

There is now ample evidence suggesting that microbes play the role of signalling components in the gut-brain axis. This emerging concept of a microbiota-gut-brain axis suggests that our ability to modulate the gut microbiota may be a potential tool towards the development of novel therapies for complex brain disorders such as psychiatric disorders[19,71,72] (Table 3).

Is there a dietary glutamate-gut-endogenous glutamate-brain axis and how can it impact depression pathogenesis?

Glutamate is a multifunctional amino acid that is involved in intermediary metabolism in the gastrointestinal tract and is also crucial for the normal functioning and development of the brain. In the gut, it is derived from exogenous sources including dietary proteins and from free glutamate present in food additives; also, a fraction of the free glutamate in the lumen is from bacterial synthesis[88]. In the central and enteric nervous systems, respectively, glutamate is the major excitatory neurotransmitter[50,89].

Glutamate and the glutamatergic pathways are also crucial to microbiota-gut-brain communication. There is increasing evidence that glutamate is both a neurotransmitter and neuromodulator of several functions[77,89]. Glutamate receptors and their transduction molecules have been demonstrated on the epithelial cells of the gut, splanchnic, vagal, and/or pelvic afferents[89-91]. The stimulation of gut glutamate receptors by dietary or luminal glutamate has been associated with the activation of vagal afferents which directly or indirectly influence brain areas such as the cerebral cortex, limbic system, hypothalamus and basal ganglia[90,92]. Also, the activation of glutamate receptors present on splanchnic, vagal, and/or pelvic afferents, allows the communication of sensory inputs to regions of the brain involved in the gut-brain axis, while, also influencing efferent pathways that convey excitatory or inhibitory inputs to the gastrointestinal tract[89,91].

While in health, the enteric ganglia and the brain are impermeable to dietary or luminal glutamate; there have been reports suggesting that glutamate permeability in these systems increases in diseased states such as enteric neuropathies, or conditions that alter the integrity of the blood-brain-barrier. The gut microbiome also influences brain glutamate, with the results of metabolomic studies revealing that alterations in the composition of the gut saprophytic microflora also affected brain concentrations of glutamate[93,94]. Although there is enough scientific evidence in support of the impact of central glutamate and the glutamatergic system in depression, there is however a dearth of information regarding the possible ways luminal glutamate (either from dietary sources or microbial activities) may influence depression pathophysiology.

However, from the foregoing, it is evident that while exogenous glutamate (from dietary sources or secreted by gut microbiota) can influence brain function through activation of the gut glutamatergic pathways, endogenous glutamate can be influenced by gut microbial composition or metabolites to impact brain function. This shows that glutamate may be more important in the bidirectional communication system of the microbiome-gut-brain axis than previously considered.

Table 3 Gut brain axis and depression

Subject	Outcome	Ref.
Germ-free mice	Germ-free (GF) mice showed impaired social interactions, anxiety and derangement of brain-derived neurotrophic factor levels	Crumeyrolle-Arias *et al*[83], Huo *et al*[85], and Kamimura *et al*[86]
GF and SPF mice	Exposure of GF mice and specific pathogen-free (SPF) mice to chronic restraint stress paradigm revealed an increase in open field exploration time in GF compared to SPF mice. Also, SPF mice exhibited more anxiety-like behavior than GF mice under the same external stress	Arentsen *et al*[84]
C57BL/6J male mice	Chronic administration of prebiotic (fructo-oligosaccharides and galacto-oligosaccharides) have been associated with antidepressant and anxiolytic effects	Kamimura *et al*[86]
Glutamate and non-glutamate supplemented media	Gamma amino-butyric acid (GABA)-producing *Lactococcus lactis* strain increased GABA production in the glutamate supplemented medium	Burokas *et al*[87]

GLUTAMATE AND DEPRESSION MANAGEMENT

In the preceding sections, the possible crucial roles that glutamate and glutamatergic neurotransmission play in the pathogenesis of mood disorders were discussed. The results of studies demonstrating the impact of glutamate dyshomeostasis and an imbalance between glutamatergic neurotransmission and synaptic plasticity on mood disorders have been pivotal in the search for novel pharmacotherapeutic strategies [51]. Also, evidence from studies demonstrating the possible antidepressant-like effects of agents acting at the glutamate receptors including NMDA receptors, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and metabotropic glutamate (mGlu) receptors are all pointers to the possible roles of glutamate and glutamate receptors in depression management.

GLUTAMATE-BASED THERAPIES IN DEPRESSION

For more than six decades, drugs that modulate biogenic amines, increasing their availability at the synaptic cleft by selectively blocking the uptake of serotonin and/or norepinephrine have been used in the management of depression. While the safety profile of the newer biogenic amine drugs has improved considerably (compared to the older monoamine oxidase inhibitors and tricyclic antidepressants), they do not address the major drawbacks that have been associated with this mechanism[95-97].

Delayed therapeutic onset, low remission rates, and increased treatment refractoriness are among the major limitations or drawbacks of the standard pharmacological agents for depression treatment[95,96]. Again, up to a third of patients are diagnosed with the treatment-resistant phenotype, adding significantly to the global burden of depression[98]. These limitations are evidence of therapeutics that were still based on an incomplete understanding of disease pathogenesis.

Evidence of ketamine's quick and relatively sustained antidepressant, anti-suicidal, and anti-anhedonic effects in treatment-resistant depression has been documented; and it represents a turning point in our understanding of the possibly crucial role that the glutamatergic system plays in depression. Such findings also prompted further research into developing novel glutamate-based therapeutic targets with better antidepressant effects and without dissociative side-effects, meaning an improvement over ketamine. The results of animal studies evaluating immobility in the forced swim test and tail suspension tests highlighted that both competitive and non-competitive NMDA receptor antagonists had antidepressant-like effects[15]. Decades later, these findings eventually culminated in the approval of esketamine (Spravato®) by the US Food and Drug Administration[99] and the European Medicines Agency[100]; esketamine was selectively approved for use (in addition to a known antidepressant) in adults with treatment-resistant MDD. Apart from this, clinical investigations also continue to affirm that a single intravenous bolus administration of ketamine can evoke a rapid (within 2 h) and lasting (up to 7 d) antidepressant action[101-103].

NMDA antagonists

Ketamine: In humans, ketamine's ability to alleviate depressive symptoms (Table 4) was first highlighted by a small, randomized, double-blind study demonstrating that a single subanaesthetic (0.5 mg/kg) dose of ketamine administered intravenously

Table 4 Glutamate-based therapies in depression

Study	Receptor type	Outcome	Ref.
Randomized, double-blind study	NMDAR antagonist	A single subanaesthetic (0.5 mg/kg) dose of ketamine administered intravenously improved depressive symptoms within 72 h in seven persons with treatment resistant major depressive disorder (MDD)	Berman *et al*[68]
Double-blind, placebo-controlled, crossover study	NMDAR antagonist	A single ketamine infusion (0.5 mg/kg over 40 min) had a rapid, robust and mildly sustained antidepressant effect (1 wk) in treatment resistant MDD	Zarate *et al*[104]
Open label study	NMDAR antagonist	Rapid anti-depressant effects of a single ketamine infusion in persons with treatment-resistant bipolar depression	DiazGranados *et al*[105]
Preclinical	NMDAR antagonist	Memantine exhibited a dose-dependent antidepressant-like response in the tail-suspension test, with the response observed at a dose of 15 mg/kg persisting with sub-chronic administration	Kitanaka *et al*[112]
Double-blind placebo controlled	NMDAR antagonist	Memantine administered at doses of between 5-20 mg/d, showed no significant effects on depression phenotypes	Parsons *et al*[110], Kos and Popik[111], and Muhonen *et al*[114]
Preclinical	NMDAR antagonist	The antidepressant effects of amantadine have been observed in situations where it is administered in combination with standard antidepressants such as fluoxetine and imipramine	Czarnecka *et al*[115] and Maj and Rogóz[116]
Preclinical	NMDA (NR2B) receptor blockers	Ro 25-6981 exhibited behavioural antidepressant-like effects in the forced swim test	Mathews *et al*[118] and Refsgaard *et al*[119]
Preclinical	NR2B-selective NMDA antagonist	CP-101,606 that was well-tolerated and devoid of psychotropic side effects was also used in a clinical trial involving subjects with traumatic brain injury	Refsgaard *et al*[119]
Randomized, placebo-controlled, double-blind study	NR2B-selective NMDA antagonist	CP-101,606 demonstrated efficacy in treatment-refractory MDD subjects	Merchant *et al*[120]
Cross-over pilot study	NR2B-selective NMDA antagonist	Oral formulation of MK-0657 in persons with treatment-resistant MDD showed a significant antidepressant effect compared with placebo while no improvement in symptoms was noted using the primary efficacy measure	Preskorn *et al*[121]
Preclinical	AMPA-antagonist	LY392098 and LY451616 exhibited antidepressant effects in a number of animal models of depression; including the inescapable stressors, learned-helplessness models, and exposure to chronic mild stress models	Li *et al*[122] and Lauterborn *et al*[123]
Preclinical	mGLu	LY341495, MSG0039, and MPEP exhibited significant antidepressant effects in rodent models of behavioural despair	Jaso *et al*[7] and Chaki *et al*[130]

NMDA: N-methyl-D-aspartate; NMDAR: N-methyl-D-aspartate receptor; AMPA: α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; mGLu: Metabotropic glutamate.

improved depressive symptoms within 72 h in seven persons with treatment resistant MDD[68]. A larger, double-blind, placebo-controlled, crossover study also found that a single ketamine infusion (0.5 mg/kg over 40 min) had a rapid, robust and mildly sustained antidepressant effect (1 wk) in treatment-resistant MDD[104]. Adverse effects that included confusion, euphoria, dizziness, perceptual disturbances, blood pressure elevation and increased libido were self-limiting[104].

Since the first clinical study that demonstrated the antidepressant effects of ketamine, several other studies have continued to examine its efficacy across other depression phenotypes[104,105]. Diazgranados *et al*[105] demonstrated the rapid anti-depressant effects of a single ketamine infusion in persons with treatment-resistant bipolar depression, which was replicated in a double-blind, randomized, crossover, placebo-controlled study[104]. The impact of ketamine on reducing suicides has also been examined. Ketamine was reported to have a rapid and significant anti-suicidal effect in persons with MDD[101]. While the discovery of ketamine's antidepressant effect was met with enthusiasm, its associated sedative and psychotomimetic effects remain limitations to its use. Therefore, efforts continue to be directed towards blunting these effects. Studies have tried to research the effects of augmenting ketamine with other drugs that are probably better-tolerated; these drugs such as riluzole and lamotrigine have been examined for their ability to either improve ketamine antidepressant effects and/or reduce its psychotomimetic effects[106-108]. However, a number of these studies reported that these add-ons showed no significant ability to improve the course of the antidepressant response (compared to ketamine alone) or reduce the side effects of ketamine[107,108]. Anand *et al*[106] on the other

hand reported lamotrigine's ability to decrease the perceptual abnormalities induced by ketamine.

Memantine and amantadine: The dampening of the enthusiasm that arose from the rapid and robust antidepressant effects of ketamine due its psychotomimetic side-effects prompted research into the possible antidepressant activities of other non-competitive NMDA receptor antagonists such as memantine, which has been reported to be devoid of these effects, at least at therapeutic doses[109-111]. The anti-depressant effects of memantine, a low-affinity, non-competitive, open-channel NMDA receptor antagonist which is approved for use in the management of Alzheimer's disease has been extensively studied [104,112]. The results of a preclinical study by Kos and Popik [111] revealed a dose-dependent antidepressant-like response in the tail-suspension test, with the response observed at a dose of 15 mg/kg persisting with sub-chronic administration. However, the results of clinical studies have shown mixed results[110, 111]. In one double-blind, placebo-controlled trial in which memantine was administered at doses of between 5-20 mg/d, no significant effects were observed [113]. This result was also supported by another double-blind placebo-controlled study that examined the effect of memantine administered at 10 mg/kg on late-onset depression[113]. However, the result of a large double-blind randomized Finnish study reported a significant antidepressant effect with memantine in persons with co-morbid alcohol dependence[114].

Amantadine is another NMDA receptor antagonist with possible influence on the serotonergic, dopaminergic and monamine-oxidase systems. The antidepressant effects of amantadine have been observed in situations where it is administered in combination with standard antidepressants such as fluoxetine and imipramine[115, 116]. However, clinical trials are limited, mostly using amantadine as an augmentation agent (up to 300 mg/daily) in treatment resistant MDD, where it had shown some modest effects[117].

Subtype-selective NMDA (NR2B) receptor blockers: Investigations into subtype-selective blockers of the NMDA receptor (Table 4) have also been undertaken to by-pass the psychotomimetic effects of ketamine. Along this line, agents such as Ro 25-6981 that can block NR2B receptors have been studied. In preclinical experiments, the NR2B antagonist Ro 25-6981 exhibited behavioural antidepressant-like effects in the forced swim test[118]. The NR2B-selective NMDA antagonist (CP-101,606) that was well-tolerated and devoid of psychotropic side effects was also used in a clinical trial involving subjects with traumatic brain injury[119].

Other selective NMDA NR2B antagonists such as MK-0657 have also been examined. Again, in a randomized, placebo-controlled, double-blind study, the anti-depressant efficacy of CP-101,606 was demonstrated in treatment-refractory MDD subjects[120], while the result of a crossover pilot study that evaluated the potential antidepressant efficacy and tolerability of an oral formulation of MK-0657 in persons with treatment-resistant MDD observed a significant antidepressant effect compared with placebo using recognized secondary efficacy scales; with no improvement noted when symptoms were assessed using the primary efficacy measure[121].

Other glutamate receptors

The AMPA glutamate receptors are main contributors in excitatory neurotransmission, as they mediate the fast, rapidly desensitizing excitation of many synapses. The potential beneficial role of AMPA receptor modulators (Table 4) in the treatment of mood disorders has been highlighted by studies that have shown that AMPA receptor potentiators such as LY392098 and LY451616 possess antidepressant effects in a number of animal models of depression; including the inescapable stressors, learned-helplessness models, and exposure to chronic mild stress models[122]. Also, they do not seem to affect the extracellular concentration of monoamines[122]; yet they enhance the neurotrophic actions of BDNF mRNA and protein in primary neuronal cultures[122,123]. However, of the AMPA receptor positive allosteric modulators being investigated for MDD treatment, ORG-26576 was amongst the most-promising until it failed Phase II trial. Currently, while the potential roles of AMPA receptor modulators in experimental models of depression are still being researched, the world is still waiting for drugs whose actions are primarily linked to this. Stimulation of the AMPA receptor has also been associated with mediating the antidepressant-like effects of ketamine and group II mGlu receptor antagonist MGS0039[124], with suggestions that increased transmission *via* glutamatergic AMPA receptors possibly provide a common mechanism of antidepressant response[51].

Kainate receptors are now recognized as important mediators of the pre- and postsynaptic actions of glutamate and GABA, through mechanisms that are still being evaluated[125]. The results of some studies have associated genetic variations in certain kainate receptor subtypes with the therapeutic outcome of antidepressant medications like citalopram and venaflaxine[125-127]. While it is generally accepted that kainate receptors have modulatory effects on synaptic transmission, the paucity of selective kainate receptor subtype agonists or antagonists has hampered research into the possible mechanisms through which kainite receptors modulate brain function and/or impact the pathogenesis and treatment of depressive disorders[125].

mGlu receptors have been shown to regulate glutamate's neuronal transmission through the ability to alter neurotransmitter release or modulate the post-synaptic responses to glutamate release. There is enough evidence from studies to support the notion that regulation of glutamatergic neurotransmission through mGlu receptors is associated with the development of mood, leading to suggestions that they could serve as novel targets in depression management[128,129]. Modulation of the mGlu receptor has also been reported to increase neurogenesis and neurotransmitter release that has now been associated with therapeutic response in humans[128]. Several mGlu2, mGlu3 and mGlu5 receptors' (Table 4) negative allosteric modulators (LY341495, MSG0039, MPEP) have been reported to have significant antidepressant effects in rodent models of behavioural despair[7,130]. Also type III mGluRs (4-8) are mostly expressed presynaptically, modulating glutamate release and response; but while a number of preclinical studies have identified possible type III mGluR novel drug targets such as the mGluR7[131,132], there is a dearth of clinical studies evaluating the possible therapeutic benefits of these type III mGluRs in depression. There have however been reports that a positive allosteric modulator of mGluR7 (AMN082) has antidepressant-like properties in rodent models of behavioural despair[7], that can be linked to its ability to modulate glutamate transmission in the hippocampus[133].

CAN THE RELATIONSHIP BETWEEN GLUTAMATE AND THE GUT-BRAIN AXIS BE OF THERAPEUTIC BENEFIT IN DEPRESSION?

There is ample evidence that dietary and endogenous glutamate (directly or indirectly) influences glutamatergic neurotransmission in the gastrointestinal tract and the brain, respectively. The gut microbiome has been shown to be involved in the synthesis and release of neuroactive molecules, including those involved in the pathogenesis of depression. Alterations in glutamate concentration and glutamatergic neurotransmission have also been linked to the pathophysiology of depressive disorders. Scientific evidence has shown that diet influences the gut microbiota composition and density, and that both diet and gut microbiota influence emotional behaviour and neurological processes[134,135]. By direct evidence and inference, we now know there is a complex interplay involving diet, the gut microbiome and depression. Hence, specific dietary patterns that can help prevent or mitigate mood disorders, possibly *via* shifts in gut microbiota equilibrium can be identified and offered as components of clinical management.

Also, the use of dietary intervention may prove to be attractive and cost-effective as an alternative or adjuvant therapy in the clinical management of depression. However, despite the tantalizing prospect, the directionality and mechanism of the relationship involving diet, the gut microbiome, and depression are still subjects of research. That being said, diets rich in vegetables, fruits, cereals, nuts, seeds, pulses and moderate amounts of dairy, eggs, fish and unsaturated fats have been associated with a lower incidence of depression[136-139], a view not supported by some studies[140,141]. Research has shown that different microbiota profiles may be associated with positive or negative mental health, emphasizing the behavioural impact of the gut microbiome. Also, if we know that behaviour is determined by the brain's neurotransmitter milieu, then the link involving diet, the gut microbiome, neurotransmitters and depression will be easier to appreciate.

Humans with depression have been shown to harbor variations in gut microbiota which tend towards a general pattern of increases in potentially harmful and inflammation promoting bacteria such as *Proteobacteria*, and a decrease in commensal bacteria, which are normally more abundant[77,141-144]. However, the lack of a specific depression-associated gut microbiota profile is a major challenge[9]. Despite this, the presence of bacteria that produce neuroactive molecules strengthens the link between gut microbiota and behavioural disorders such as depression. *In vitro* and *in vivo* studies have demonstrated the ability of intestinally cultured strains of *Lactoba-*

cillus brevis and *Bifidobacterium dentium* to efficiently produce GABA from monosodium glutamate enriched medium or monosodium glutamate supplemented food, respectively[145,146]; leading to suggestions that this could represent a promising therapeutic approach for depression management. Also, *Lactobacillus rhamnosus* (JB-1) has been shown to reduce stress-induced corticosterone levels in mice and ameliorate depression-like behaviour in the forced swim test; while also increasing brain glutamate and glutamatergic activity[9]. Other specific relationships involving glutamate are still being investigated, and their direct implications for therapy are being considered.

CONCLUSION

The limitations of the amine theory redirected the research focus to what was supposedly missing in the scientific understanding of the aetiology, course and management of depression. The discovery of the antidepressant effect of ketamine brought attention to the impact that manipulation of the glutamatergic system can have on the management of depression. Also, the role of diet and the gut microbiome in glutamate homeostasis is being continuously examined. As it becomes evident that gut microbes are involved in the synthesis and secretion of molecules that directly impact the brain, including glutamate, we now know that their manipulation through diet can become a cornerstone for the prevention and management of behavioural disorders. However, while glutamate-based therapies for depression are still in their infancy (and much more is dietary manipulation of glutamate balance *via* the gut microbes), it appears that understanding the diet, gut microbiome, gut-brain axis and glutamate link may be the next frontier in advancing our understanding of depression.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 316-324

DOI: 10.5498/wjp.v11.i7.316

ISSN 2220-3206 (online)

MINIREVIEWS

Selective serotonin reuptake inhibitors and risk reduction for cardiovascular disease in patients with schizophrenia: A controversial but promising approach

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Author contributions: Nguyen K wrote the first draft and collected most of the information included in this manuscript; Bellon A envisioned and designed this manuscript, then retrieved further essential information and wrote the final draft.

Conflict-of-interest statement: The authors report no conflict of interest related to this manuscript.

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Manuscript source: Invited manuscript

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Abstract

Patients with schizophrenia (SCZ) are at high risk of cardiovascular disease (CVD) due to an inherited predisposition, a sedentary life style and the use of antipsychotic medications. Several approaches have been taken to minimize this risk but results continue to be unsatisfactory. A potential alternative is prescribing selective serotonin reuptake inhibitors (SSRIs). SSRIs decrease platelet aggregation and reduce the risk of coronary heart disease in patients with depression. We therefore aim to investigate whether there is evidence that supports the use of SSRIs to reduce the risk for CVD in SCZ. A review of the literature revealed five published reports relating to the impact of SSRIs on CV risk in SCZ. Three trials assessed the influence on metabolic parameters of fluvoxamine when combined with clozapine. Two of those studies found improvements with fluvoxamine. Of the other two reports, one indicates SSRIs as a group caused minimal but statistically significant increments in total cholesterol, low-density lipoprotein and triglyceride. The second report suggests that when SSRIs are combined with antipsychotics, the metabolic impact depends on the antipsychotic prescribed. While there are promising results, no conclusions can be made currently on whether SSRIs increase or decrease CV risk in SCZ. Further studies are needed to resolve this matter.

Key Words: Antidepressants; Metabolic syndrome; Cholesterol; Psychotic disorders; Antipsychotics; Body weight

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Specialty type: Psychiatry

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 17, 2020
Peer-review started: December 17, 2020
First decision: March 30, 2021
Revised: May 16, 2021
Accepted: June 28, 2021
Article in press: June 28, 2021
Published online: July 19, 2021

P-Reviewer: Dimopoulos N
S-Editor: Zhang L
L-Editor: A
P-Editor: Li JH

Core Tip: We searched MEDLINE and Google Scholar to find articles related to the cardiovascular effects of selective serotonin reuptake inhibitors (SSRIs) in patients with schizophrenia (SCZ) who are taking antipsychotics. We found evidence showing that fluvoxamine reduces metabolic factors in patients taking clozapine, but we also found that SSRIs as a group cause significant yet small increments in metabolic factors. There is also evidence that the effect of SSRIs on metabolic factors depends on which antipsychotics the patient is concurrently taking. Further research in this area is needed before any firm conclusion can be reached on whether SSRIs are beneficial or harmful for cardiovascular risk in SCZ.

Citation: Bellon A, Nguyen K. Selective serotonin reuptake inhibitors and risk reduction for cardiovascular disease in patients with schizophrenia: A controversial but promising approach. *World J Psychiatr* 2021; 11(7): 316-324
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/316.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.316

INTRODUCTION

Life expectancy of patients with schizophrenia (SCZ) is significantly lower than for the rest of the population[1]. While multiple factors are at play, a common culprit is cardiovascular disease (CVD)[2-5]. The risk for CV illness is compounded by several characteristics surrounding SCZ, such as an inherited predisposition to develop metabolic abnormalities[6] and the fact that patients often experience apathy and anhedonia, symptoms that lead to a sedentary lifestyle. In addition, high rates of smoking and diets rich in calories and fat are also common among patients with SCZ [7]. But perhaps even more significant is the impact of antipsychotics, particularly second-generation antipsychotics. These medications induce weight gain, hyperlipidemia and diabetes[8] all risk factors for CVD.

Mitigation of CV risk in patients with SCZ already includes a polydimensional approach that considers promoting changes in life style such as increased exercise and improved diet, switching or reducing the dose of antipsychotic medications[8], as well as the potential use of statins[9] and metformin[10]. But according to a recent meta-analysis, all these efforts continue to fall short of a desirable outcome[1]. In the general population, patients at risk for CVD are often placed on aspirin or an anticoagulant like clopidogrel, but these medications are associated with increased risk of bleeding [11] and thus guidelines for their use are becoming more restrictive[11]. A potential alternative is the use of selective serotonin reuptake inhibitors (SSRIs). SSRIs decrease platelet aggregation and appear to have a lower risk of bleeding than other anticoagulants[12,13]. Moreover, there is evidence indicating that SSRIs can reduce the risk of coronary disease[14] and lower the severity of ischemic strokes[15]. Therefore, our hypothesis is that SSRIs could be a safe alternative to reduce the risk of CVD in patients with SCZ taking antipsychotics.

In order to challenge our hypothesis, we first present evidence indicating patients with SCZ are at an increased risk of CVD. Second, we review emerging data on the impact of SSRIs for CV risk and third, we describe and discuss currently available published literature on the role SSRIs have on CVD in patients with SCZ.

A review of the literature was conducted *via* MEDLINE and Google Scholar using search terms such as SCZ, SSRIs, CV risk, metabolic abnormalities, metabolic syndrome and morbidity. The search was limited to studies published in English. For each of the scientific manuscripts identified relating to the impact of SSRIs on metabolic or CV risk in patients with SCZ, its references were thoroughly inspected for secondary publications.

Schizophrenia and Cardiovascular risk

Patients with SCZ appear to have an inherited predisposition to develop risk factors for CVD. For instance, drug-naïve patients have greater than three times as much intra-abdominal fat as age-and body mass index (BMI)-matched individuals[16]. They also have impaired fasting glucose tolerance and are more insulin resistant than healthy subjects[6]. In addition, apathy and anhedonia are symptoms commonly experienced by patients with SCZ. These symptoms lead to limited physical activity

which in combination with high intake of fat and sugar often seen in SCZ, ultimately result in the development of metabolic syndrome[7]. Metabolic syndrome understood as dyslipidemias, insulin resistance and elevated blood glucose, frequently results in diabetes mellitus type 2 and CVD[17]. Not surprisingly, the prevalence of both diabetes and obesity is two to four times higher in patients with SCZ than in the general population[18]. Another contributing factor for the high prevalence of diabetes and the increased risk for CVD is antipsychotic intake.

All antipsychotics, including older typical neuroleptics, can elicit metabolic abnormalities[8,19]. The rate at which these side effects occur however, differs among medications. In the typical antipsychotic class, lower potency antipsychotics such as chlorpromazine and thioridazine induce greater weight gain compared to higher potency antipsychotics such as fluphenazine and haloperidol[20]. Likewise, chlorpromazine and thioridazine are more strongly associated with diabetes compared to other typical antipsychotics[21]. But comparisons between typical *vs* atypical antipsychotics, also known as second generation antipsychotics (SGA), have clearly shown that SGA are more commonly associated with metabolic side effects[22]. Among SGA, clozapine and olanzapine appear to have the strongest association with weight gain and diabetes [23,24]. Quetiapine is not far behind in its ability to elicit metabolic dysregulations. According to the clinical antipsychotic trials of intervention effectiveness study[25], olanzapine and quetiapine are associated with increases in total cholesterol and triglyceride (TG) levels. When ranked for its potential to cause weight gain and other metabolic abnormalities, clozapine and olanzapine are at the top of the list followed by quetiapine and risperidone, while aripiprazole and ziprasidone are found at the bottom of the ranking[23,26,27]. For those medications with higher risk, data indicates there is a dose-dependent relationship between dose and metabolic complications[28]. For aripiprazole and ziprasidone no such relationship has been found[28]. Newer antipsychotics such as lurasidone, cariprazine and paliperidone are poorly studied to date.

SSRIs and Cardiovascular disease

Serotonin is needed for platelets to elicit platelet aggregation and vasoconstriction[29]. Platelets rely on reuptake of serotonin as they lack the capacity to synthetize this amine[29]. By inhibiting serotonin reuptake in platelets, SSRIs alter hemostasis[12,13] and therefore, are associated with increased risk for bleeding[30]. This potentially serious side effect however, is most commonly observed in individuals with medical conditions that already carry an increased risk of bleeding[13] or those taking other anticoagulant medications[30]. Overall, SSRIs are safe medications that rarely cause any serious side effects[31].

In the context of CVD, disrupting platelet aggregation could become an advantage. Not surprisingly, several studies have tried to establish whether SSRIs can minimize the risk of CV events. The majority of these publications indicate that SSRIs are cardioprotective in patients with depression (For a review refer to Andrade *et al*[9] and a recent meta-analysis by Guo *et al*[32]) but inconsistencies remain[9,33]. Variations in the cardioprotective effects of SSRIs could be related to differences in its mechanism of action. While all SSRIs diminish vasoconstriction and platelet aggregation by lowering serotonin release in platelets, other signaling cascades are also at play. For instance, sertraline impairs platelet aggregation by inhibiting CD9, GPIb, GPIIb/IIIa surface receptors while its inactive metabolite, N-desmethylsertraline, targets P-selectin and platelet endothelial cell adhesion molecule-1[12]. Sertraline also diminishes E-selectin and β-thromboglobulin concentrations[34]. In contrast, citalopram, fluvoxamine and fluoxetine inhibit tumor necrosis factor (TNF)-α-induced expression of vascular cell adhesion molecule and intracellular adhesion molecule in human aorta endothelial cells and TNF-α-stimulated adhesiveness to monocytes, resulting in less inflammation and more cardioprotective effects in patients with heart disease[35].

Recent clinical data also indicates there are differences in the potential CV benefits offered by SSRIs. Escitalopram appears to be the most advantageous for CV safety in older individuals at risk of coronary heart disease, whereas fluoxetine provided little benefit if at all[32]. In this same study, sertraline, citalopram and paroxetine delivered better caridoprotection than fluoxetine but less than escitalopram[32].

In addition to its effects on platelet aggregation and vasoconstriction, SSRIs could also impact metabolic markers. Diagnosis appears to be an important factor determining the role of SSRIs on metabolic markers. For instance, several studies have shown that SSRIs increase cholesterol levels in patients with panic disorder[36-38] with paroxetine being the main offender[37,38]. For women with generalized anxiety disorder (GAD) the impact varies according to the SSRI taken. Paroxetine increased BMI, waist circumference, fasting glucose, total cholesterol, low-density lipoprotein

(LDL), and TG after 16 wk, while citalopram and escitalopram only resulted in higher TG levels[39]. This study involving women with GAD also found that sertraline elevated total cholesterol, in contrast, fluoxetine lowered total cholesterol, weight and TG[39]. Similarly, adding fluoxetine to olanzapine for patients with bipolar depression did not affect cholesterol levels or body weight (BW) when compared to treatment with olanzapine alone[40].

SSRIs and Cardiovascular risk in Schizophrenia

The first study to assess the metabolic impact of SSRIs in SCZ is a randomized, prospective trail published in the year 2000 (Table 1)[41]. The authors tested whether clozapine alone or in combination with fluvoxamine differentially impacted BW, BMI or leptin levels among other parameters during a 6-wk follow-up period. They found no changes in weight or BMI between groups. Leptin levels however, were higher in patients receiving the combined therapy. Levels of clozapine, norclozapine or the ratio norclozapine-clozapine were similar between cohorts. Eleven patients received the dual therapy while 12 patients were prescribed only the antipsychotic. Fluvoxamine was prescribed at either 50 or 75 mg/d while clozapine was given at doses of 100 to 150 mg/d in the combined group and around 300 mg/d for patients receiving clozapine alone.

The second study on SSRIs, CV risk and SCZ is a prospective, randomized, open-label study that also compared clozapine monotherapy *vs* clozapine with fluvoxamine (Table 1)[42]. The medications were prescribed at slightly different doses than on the previous trail. The monotherapy group received up to 600 mg/d of clozapine, whereas the combined group could only take up to 250 mg/d together with fluvoxamine 50 mg/d. The rationale was that fluvoxamine increases the serum clozapine level 2.3 times[43]. Sixty-eight patients were recruited, thirty-four for each group. The authors assessed BW weekly during the 12-wk follow-up period. Fasting glucose, cholesterol and TG were measured at baseline and then at the end of the study. Their results showed that clozapine significantly increased weight, BMI, blood sugar and TG when baseline numbers were compared to values obtained after 12 wk. Comparisons between groups, revealed that individuals receiving clozapine alone had higher levels of blood sugar and TG by the end of the follow-up period. The authors also found that levels of norclozapine correlated with elevated blood sugar and TG while levels of clozapine did not. It is important to note that this study was conducted entirely with inpatients and therefore, their food intake was restricted to a hospital diet.

Lu *et al*[44] followed their open-label study on the metabolic effects of fluvoxamine in patients taking clozapine with a double-blind, randomized, clinically controlled trial (Table 1). Eighty-five patients were recruited and followed for 12 wk, with 43 receiving clozapine monotherapy at a target dose of 300 mg/d and 42 given fluvoxamine at 50 mg/d and clozapine at 100 mg/d. The authors found that the clozapine-fluvoxamine combination limited increments in BW and waist circumference and reduced levels of insulin resistance, blood glucose, cholesterol and TG when compared with clozapine monotherapy. The Positive and Negative Symptoms Scores also improved on the dual therapy cohort. Liquid chromatography revealed no differences in blood levels of clozapine but, levels of norclozapine and clozapine N-oxide were higher on the monotherapy group. The norclozapine-clozapine ratio was higher in the combination group.

Through a naturalistic, cross-sectional study, Fjukstad *et al*[45] aimed to determine the effects of SSRIs on total cholesterol, LDL, high-density lipoprotein (HDL), TG, glucose, BMI, waist circumference and blood pressure. Their database included 868 patients with SCZ of whom 169 were taking SSRIs and 433 individuals with bipolar disorder of whom 111 were taking SSRIs (Table 1). Linear regression analyses, indicated that SSRIs caused minimal but statistically significant increments in total cholesterol, LDL and TG. The authors also found that patients taking SSRIs had a slightly higher risk for developing metabolic syndrome. Blood glucose, BMI, waist circumference and blood pressure were not affected by the use of SSRIs. Unfortunately, the authors did not parcel patients by diagnosis. Potential differences among the different SSRIs included in the analysis namely, escitalopram, citalopram, sertraline, fluoxetine and paroxetine were not investigated.

This research group published a second study mining the same cohort of patients (Table 1)[46]. Their new objective was to determine whether adding SSRIs to antipsychotic medications would increase metabolic risk factors[46]. Three antipsychotics were included in their analysis, olanzapine, quetiapine and risperidone. SSRIs added to olanzapine or quetiapine led to small but statistically significant elevations in total cholesterol and LDL. Blood glucose increased when olanzapine was given together with SSRIs, in contrast, combining risperidone with SSRIs led to lower blood

Table 1 Selective serotonin reuptake inhibitors and cardiovascular risk in patients with schizophrenia

Ref.	SSRI studied	Number of patients	Sex	Average age	Duration	Metabolic parameters
Hinze-Selch *et al* [41], 2000	Fluvoxamine[1]	23	M: 11 F: 12	32 ± 15[1]	6 wk	BW, BMI, Leptin
Lu *et al*[42], 2004	Fluvoxamine[1]	68	M: 20 F: 48	32.9 ± 8.5[1]	12 wk	BW, BMI, Glucose, Total Cholesterol, TG
Fjukstad *et al* [45], 2016	Escitalopram, citalopram, sertraline, fluoxetine and paroxetine	868[2]	M: 697 F: 604	31.7 ± 10.6	Cross sectional study	Total Cholesterol, LDL-C, HDL-C, TG, WC, SBP, DBP, BMI, Glucose
Lu *et al*[44], 2018	Fluvoxamine[1]	85	M: 61 F: 24	43.6 ± 8.1	12 wk	SBP, DBP, BW, WC, Insulin, FPG, Uric Acid, Total Cholesterol, TG, HDL-C, LDL-C, HOMA-IR
Fjukstad *et al* [46], 2018[3]	Escitalopram, citalopram, sertraline, fluoxetine and paroxetine	868[2]	M: 697 F: 604	31.7 ± 10.6	Cross sectional study	Total Cholesterol, LDL-C, HDL-C, TG, WC, SBP, DBP, BMI, Glucose

[1]In combination with clozapine.
[2]the authors also included 433 individuals with bipolar disorder.
[3]The authors studied SSRIs combined with olanzapine, quetiapine and risperidone.
SSRI: Selective serotonin reuptake inhibitors; BW: Body weight; BMI: Body mass index; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglyceride; SBP: Systolic Blood Pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; HOMA-IR: Homeostasis model assessment of insulin resistance.

glucose. The authors reported that none of the other parameters studied were affected by coadministration of risperidone and SSRIs. Dual therapy with SSRIs and either olanzapine or quetiapine also did not alter HDL, TG, BMI or blood pressure. What the authors did not mention but appears to be evident from their figures, is that risperidone alone led to statistically higher levels of LDL but when prescribed in conjunction with SSRIs, LDL did not increase. Likewise, quetiapine monotherapy caused a modest but statistically significant elevation in TG, while in combination with SSRIs TG did not change. Quetiapine without SSRIs significantly increased BMI but with these antidepressants, BMI was unaffected. The authors emphasized that their results have to be pondered with caution as their methodology did not allow excluding the potential impact of diet and even more importantly, they did not have access to non-psychotropic medications being taken by their patients such as statins or insulin.

CONCLUSION

Several factors place individuals with SCZ at risk of CVD including an inherited predisposition to metabolic anomalies[6,16], a sedentary life style prompted at least in part by core symptoms of this psychotic disorder and the use of antipsychotic medications which elicit metabolic syndrome[8]. So far, attempts to reduce all these risk factors have rendered unsatisfactory results[1]. Therefore, the search for new approaches continues.

Because of their capacity to decrease platelet aggregation and vasoconstriction[12,13], SSRIs have been investigated as a potential alternative. Specially, considering that SSRIs have delivered promising cardioprotective results when prescribed for other mental illnesses such as major depressive disorder[9,14]. In addition to its effects on hemostasis, SSRIs can also influence CV risk by altering metabolic markers such as total cholesterol, LDL, BMI, blood glucose and others. But in contrast with its effects on platelet aggregation and vasoconstriction which are directly linked to SSRIs ability to block serotonin[12,13], how these medications elicit changes in metabolic parameters is yet undetermined. What the evidence currently indicates is that SSRIs impact on CV risks varies according to diagnosis and the specific SSRI prescribed. For instance, the risk for CVD is likely to increase if patients with panic disorder take paroxetine[36-38]. Gender also has to be considered. If women with GAD receive paroxetine, their likelihood of developing CVD also augments[39]. Conversely, fluoxetine has a cardioprotective effect on women with GAD[39]. Age also appears to be a factor. Older individuals at risk of coronary heart disease obtain no benefit from

receiving fluoxetine, whereas, escitalopram can be advantageous[32].

Not surprisingly, how SSRIs affect CV risk in patients with SCZ also depends on which specific one is being prescribed. Two trials developed by the same research team have shown that fluvoxamine diminishes at least some of the metabolic side effects elicited by clozapine[42,44]. These two studies took important steps to limit potential confounding factors such as excluding individuals taking medications known to affect metabolic parameters and at least one of those trails controlled their cohort's food intake. There is also one publication that encountered different results. An independent team that also assessed the effects of fluvoxamine coadministered with clozapine did not find any metabolic benefits[41]. It is possible that the short duration of this study of only 6 wk could have prevented the authors from finding any significant differences. The two studies that found fluvoxamine to be effective, lasted for 12 wk. All three studies measured blood levels of clozapine and its metabolites and two of them found norclozapine levels to be associated with metabolic abnormalities. The three trials recruited a relatively small number of patients (Table 1).

The first cross-sectional study that Fjukstad *et al*[45] published found that SSRIs increased total cholesterol, LDL and TG in patients with SCZ and bipolar disorder. Nonetheless, there are several confounding factors that have to be pondered when assessing these results. Their study design did not allow discrimination of metabolic parameters between patients with SCZ and bipolar disorder as they were considered a single cohort. Likewise, escitalopram, citalopram, sertraline, fluoxetine and paroxetine were all clustered together in the analysis and consequently its potential individual impact could not be determined. Diet was not controlled for either this or their second study discussed below. Also applicable for both studies is that the authors did not have access to other medications their patients may have been taken such as statins or insulin which could ultimately impact their results.

Fjukstad *et al*[46] second cross-sectional study presents intriguing results consistent with previous publications suggesting that SSRIs influence the metabolic impact of antipsychotics in patients with SCZ. The authors found that when olanzapine is combined with an SSRI, several metabolic parameters worsened. Similarly, the combination of quetiapine and SSRIs leads to increases in total cholesterol and LDL. But this dual therapy prevents increments in TG and BMI caused by quetiapine alone. SSRIs appear to be beneficial when taken with risperidone. This combination lowers blood glucose and prevents rises in LDL elicited by risperidone monotherapy. Unfortunately, whether each of the SSRIs studied affects metabolic markers differently, was not determined, as all SSRIs included in the analysis were clustered as one group (Table 1).

SSRIs could improve CV risk by another mechanism of action. One of the factors that place patients with SCZ at increased CV risk is a sedentary life style. Negative symptom of SCZ can significantly contribute to lower levels of psychical activity. Thus, successfully treating negative symptoms would lead to benefits in CV health. Antidepressants have been successfully used in treating negative symptoms of SCZ, though not always[47].

The information currently available does not allow us to draw any firm conclusions. However, it suggests that for patients with SCZ, adding fluvoxamine to clozapine brings metabolic benefits[42,44], though clinicians have to be cautious with this combination as fluvoxamine can drastically increase clozapine levels[43]. Similarly, dual therapy with risperidone and SSRIs also appears to improve some metabolic parameters[46] but whether a specific SSRI is more advantageous than others is yet to be established. What appears to be clear is that SSRIs impact CV risk by affecting metabolic markers and that each SSRI has its own unique metabolic advantages and disadvantages depending on gender, age, diagnosis and the presence or absence of antipsychotics. Therefore, when metabolic parameters are being studied, SSRIs should be considered a confounder. Also evident is that no conclusions can be made currently on whether SSRIs increase or decrease CV risk in patients with SCZ. Further studies are needed to resolve this matter.

ACKNOWLEDGEMENTS

The authors would like to thank the Ling and Esther Tan Early Career Professorship endowment given to AB. We are also grateful for the thorough editorial comments from Professor Andrew Francis.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 325-336

DOI: 10.5498/wjp.v11.i7.325

ISSN 2220-3206 (online)

MINIREVIEWS

Risk factors for antenatal depression: A review

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Author contributions: Míguez MC and Vázquez MB developed the framework of the paper; Vázquez MB carried out the literature searches and wrote the first draft; all authors worked on subsequent drafts, confirmed the last version before submission, and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Spain

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Abstract

Depression is the most prevalent mental disorder in pregnancy, and yet it is less studied than postpartum depression despite the consequences it may have on both the pregnant woman and her offspring. Therefore, it would be important to know which risk factors may favour the appearance of antenatal depression in order to carry out appropriate prevention interventions. The aim of the present review was to identify the main risk factors of antenatal depression. We searched in databases PubMed and PsycINFO for articles published about the factors associated with antenatal depression from January 2010 through December 2020. The literature review identified three main groups of antenatal depression risk factors: sociodemographic, obstetric, and psychological. First, among the sociodemographic variables, the low level of studies and the economic income clearly stood out from the rest. Then, not having planned the pregnancy was the main obstetric variable, and finally, the main psychological risk factors were having a history of psychological disorders and/or depression as well as presenting anxiety, stress, and/or low social support during pregnancy. This review shows that the antenatal depression is affected by multiple factors. Most can be identified at the beginning of the pregnancy, and some are risk factors potentially modifiable through appropriate interventions, such as psychological factors. For this reason, it is important to carry out a good screening for depression during pregnancy and consequently, be able to prevent its appearance or treat it if necessary.

Key Words: Depression; Antenatal; Antenatal depression; Pregnancy; Risk factors; Review

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Core Tip: Depression is the most prevalent mental disorder in pregnancy and is caused by multiple factors. This review article shows that sociodemographic, obstetric, and

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 5, 2021
Peer-review started: February 5, 2021
First decision: March 8, 2021
Revised: March 20, 2021
Accepted: May 20, 2021
Article in press: May 20, 2021
Published online: July 19, 2021

P-Reviewer: Wang MZ
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Xing YX

psychological factors are associated with the presence of antenatal depression. Most of them can be identified in early pregnancy. Therefore, a complete medical history along with the routine use of screening instruments to detect the risk profile of these women would allow the prevention and early detection of antenatal depression.

Citation: Míguez MC, Vázquez MB. Risk factors for antenatal depression: A review. *World J Psychiatr* 2021; 11(7): 325-336
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/325.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.325

INTRODUCTION

Traditionally, it was thought that pregnancy protected women against the onset or relapse of a depressive disorder. However, it has been shown that pregnancy does not protect them, and together with postpartum are two periods of great vulnerability for women[1]. Some studies have found that antenatal depression is as frequent, or even more frequent than postpartum depression[2-4]. Still, it is often underdiagnosed and, as a consequence, undertreated[5]. Furthermore, antenatal depression constitutes a major public health problem[6] due to the reasons discussed below.

Despite the fact that many women remain undiagnosed[7], the prevalence of depression during pregnancy is high[8,9] and varies in the different trimesters across studies[8,10,11].Therefore, diagnosing antenatal depression can be difficult if women are only screened once throughout pregnancy.

Depression during pregnancy has received much less attention than postpartum depression, although in the last decade the study of antenatal depression is becoming more and more prominent. This may be due to either an increase in diagnosed cases of depression in pregnant women or to the acquisition of greater awareness of the consequences of antenatal depression[12] among professionals.

During pregnancy, depression has a negative impact on both the course of pregnancy and on the foetal and neonatal outcome[13-15], with growing research in the field of "foetal programming," triggering interest in the study of depression during pregnancy. According to this theory, the perinatal period is a critical stage where mental health protection efforts should be focused, and prevention models be developed[16]. It is now known that the psychological state of a mother during pregnancy has an important impact on the subsequent development and health of her child[15]. In this regard, the association between maternal stress, depression, or anxiety in pregnancy and an adverse neurodevelopmental outcome of the child is evident[17]. In addition, studies focusing on the perinatal period found that depression during pregnancy is the most important risk factor for postpartum depression[18,19].

Reviews identifying risk factors associated with prenatal depression are scarce and focus on a few risk factors, analyze them separately[20-22], or in a particular country/culture[23]. In light of the foregoing, it would be important to identify the risk factors associated with the presence of antenatal depression from the beginning of pregnancy, as this would allow us to offer more efficient help in accordance with the needs of future mothers, improving their self-perception of well-being. This would also prevent this depressive state from extending to the postpartum period, with the consequences that this would entail for both mothers and their children.

Therefore, the objective of this review is to describe and group the main risk factors found in the studies published in the last 10 years that simultaneously may be associated with the presence of antenatal depression.

LITERATURE REVIEW

A literature search was performed in PsycINFO and PubMed databases, using the search string: "antenatal depression" OR "depression during pregnancy" AND "risk factors" OR "variables associated." The literature search was restricted to studies written in the English language and published from January 2010 to December 2020. Reference lists from retrieved articles were also examined.

INCLUSION AND EXCLUSION CRITERIA

The variables/risk factors associated with antenatal depression were the epidemiological parameters of interest. Studies were included as long as they made use of population-based surveys representative of communities, regions, or countries under study. Non-representative samples (*e.g.*, inpatient groups, minority populations, victims of gender-based violence, immigrants, with presence of concomitant medical conditions, at risk of social exclusion) were excluded as they would probably provide biased estimates of risk factors associated with antenatal depression in the general population. Finally, studies using screening instruments (*e.g.*, Edinburgh Postnatal Depression Scale, Patient Health Questionnaire, Beck Depression Inventory) and structured interviews (*e.g.*, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders) for diagnosis were included.

RESULTS AND DISCUSSION

Details of results are presented in Table 1. Out of the 466 titles identified on risk factors of antenatal depression, 29 studies met inclusion criteria. The analysis of the literature showed that the factors associated with antenatal depression can be classified into three domains of risk factors: sociodemographic, obstetric, and psychological risk factors. Although some variables are related to lifestyle, such as weight and substance use, they are also mentioned in several studies. In the studies, when information was available, the level of significance of the association (*P* value) and the odds ratio of the predictor variables are shown with the objective of showing the strength of the association between variables.

The variability of risk factors associated with antenatal depression found across studies can be attributed to several reasons. First, different instruments are used for assessing antenatal depression. More specifically, 27 studies assessed antenatal depression with self-reported questionnaires, with the Edinburgh Postnatal Depression Scale being the most commonly used (n = 16). However, with different cut-off points across countries, even in studies carried out in the same country[24-26]. Only 2 studies used clinical interviews for diagnosis. In this regard, women may overestimate or underestimate their responses to a self-report questionnaire based on their beliefs, perceptions, culture, and stigmatisation of mental health in their communities[27]. It is also important to consider cultural differences, as they may explain part of the variability of some of the risk factors [for example, the type of public and/or private health care, prenatal health care and the ease of access, the professionals who monitor the pregnancy (*e.g.*, gynaecologists, midwives, nurses), the quality of care available, religious customs, attitudes towards pregnancy and motherhood, gender roles, and/or the role of women in making decisions about her pregnancy][27].

Of the 29 studies included in this review, Arab countries contributed with the largest number of articles (n = 8), followed by Europe (n = 6), Asia (n = 5), Brazil (n = 4), Africa (n = 3), Australia (n = 3), and India (n = 1). The samples of these studies were obtained from women who attended their follow-up pregnancy check-ups at their health centres of reference.

Particularly, there are 15 cross-sectional/cohort studies and, hence, evaluated women at any time regardless of their gestational age; 10 studies included women in their third trimester of pregnancy, and 4 studies evaluated women in their first trimester. No studies were found that analyzed risk factors associated with antenatal depression by trimester. The absence of studies that separately identify the risk factors associated with antenatal depression by trimester may offer a biased information on these variables. This is because each trimester of pregnancy has specific characteristics because both the physical changes, the medical tests, and the concerns that pregnant women face vary throughout the gestation. Therefore, variables that in a given trimester could be significantly related to antenatal depression (*e.g.*, being in the first trimester and having had previous abortions) are perhaps not if women are evaluated in another trimester.

Sociodemographic variables

Different sociodemographic variables have been evaluated in the scientific literature (*e.g.*, age, marital and employment status, educational level, *etc.*). In this section, we will present those most studied in relation to the presence of depression during pregnancy.

Table 1 Risk factors for antenatal depression

Ref.	Sociodemographic variables	Obstetric variables	Psychological variables
Benute *et al*[41], 2010, Brazil	Low Socioeconomic S. (0.04)	U. pregnancy (0.04)	
Kheirabadi and Maracy[12], 2010, Iran	Being a housewife[1] 2.28	U. pregnancy[1] 1.62	Previous depression[1] 1.83
	Age < 25-yr-old[1] 1.53	Multiparity[1] 2.35	
Banti *et al*[10], 2011, Italy	Low Socioeconomic S.[1] 2.48	Multiparity[1] 1.95	Anxiety (pregnancy)[1] 4.10
Husain *et al*[38], 2011, Pakistan	Low Socioeconomic S.[1] 1.40	Complications in a previous delivery[1] 0.98	
	Low Educational L.[1] 1.28		
	Unemployed husband[1] 1.73		
	Nuclear family[1] 1.18		
Mohammad *et al*[46], 2011, Jordan	Marital dissatisfaction (0.002)	U. pregnancy[1] 0.08	Anxiety[1] 0.13
	Concern about the economic situation[1] 0.08	Lack of knowledge about parenting[1] 0.16	Stress[1] 0.41
		Lack of maternal ability[1] 0.27	Low social support (0.001)
Giardinelli *et al*[47], 2012, Italy	Foreign nationality[1] 3.34	U. pregnancy[1] 3.83	Previous psychiatric disorders[1] 3.11
	Unemployment[1] 2.17		
	Marital dissatisfaction[1] 4.20		
Goecke et *al*[37], 2012, Germany	Low Educational L. (0.001)	Miscarriages (0.016)	
Melo *et al*[25], 2012, Brazil	Low Socioeconomic S.[1] 1.75	Multiparity[1] 1.32	
	No partner[1] 1.93		
	Non-White race[1] 1.48		
Ajinkya *et al*[6], 2013, India		U. pregnancy (0.019)	
		Previous obstetric complications (< 0.001)	
		Obstetric complications (< 0.001)	
		Miscarriages (< 0.001)	
		Multiparity (< 0.01)	
Bödecs *et al*[23], 2013, Hungary	Low Socioeconomic S. (< 0.05)		
	Low Educational L. (< 0.05)		
	Unemployment (< 0.01)		
	Age < 20-yr-old (< 0.05)		
Fadzil *et al*[56], 2013, Malaysia		Previous cesarean section (0.042)	Anxiety (pregnancy) (0.006)
Yanikkerem *et al*[39], 2013, Turkey	Low Educational L.[1] 1.49	U. pregnancy[1] 1.41	Low social support[1] 2.42
		Physical symptoms during pregnancy[1] 0.68	
Weobong *et al*[34], 2014, Australia	Age > 30-yr-old[1] 1.16	U. pregnancy[1] 1.55	
	No partner[1] 1.34	Miscarriages[1] 1.30	
Brittain *et al*[42], 2015, South Africa	Low Socioeconomic S.[1] 1.03	U. pregnancy[1] 2.0	Previous history of gender violence[1] 1.9
	No partner[1] 1.7		Stressful life events[1] 1.9
Waldie *et al*[15], 2015, Australia	Non-European race[1] 1.90-2.35	U. pregnancy[1] 1.30	Perceived stress (pregnancy)[1] 1.34
			Anxiety before and during pregnancy[1] 3.08
Al-Azri *et al*[48], 2016, Oman	Marital dissatisfaction[1] 13.83	U. pregnancy[1] 1.37	Family depression (0.019)
Castro e Couto *et al*[26], 2016,		Multiparity (0.02)	Previous depression[1] 11.32

Brazil	Low Educational L. (0.022)		Gender violence[1] 2.66
Thompson and Ajayi[33], 2016, Nigeria	Maternal age 15-20-yr-old (0.012)	U. pregnancy (0.014)	Gender violence[1] 3.90
		Obstetric complications (0.034)	
	No partner (0.010)	Previous cesarean (0.032)	
	Increased number of family members (0.029)		
	Drinking alcohol (pregnancy)[1] 3.98		
Weng *et al*[11], 2016, China	Low Socioeconomic S.	U. pregnancy	Previous depression
	Passive smoking		Poor sleep quality
	No partner		
Coll *et al*[24], 2017, Brazil	Low Educational L.[1] 5.47	Multiparity[1] 2.56	Previous depression[1] 2.93
	Age < 35-yr-old[1] 1.36		
	No partner[1] 1.36		
Redinger *et al*[50], 2018, South Africa	Marital dissatisfaction (< 0.05)	Nulliparity (< 0.05)	Current psychiatric disorders (< 0.05)
			Stressful family events[1] 2.41
			Anxiety (< 0.05)
Yu *et al*[72], 2017, China			Poor sleep quality 1.54
González-Mesa *et al*[52], 2018, Spain	Unemployment[1] 1.34	U. pregnancy[1] 2.78	
		Miscarriages[1] 1.67	
Turkey	Unemployment[1] 1.34	Multiparity[1] 0.81	
Ogbo *et al*[43], 2018, Australia	Low Socioeconomic S.[1] 0.3-0.6		Low partner support[1] 8.5
	Living in a multiethnic population[1] 1.8		Gender violence[1] 6.0
Pampaka *et al*[44], 2018, Kuwait	Low Socioeconomic S.[1] 1.69		Previous depression[1] 4.35
Al-Hejji *et al*[73], 2019, Saudi Arabia	Husband smoker[1] 1.43	Multiparity[1] 1.87	Poor sleep quality[1] 1.88
			Post-miscarriage psychological complications[1] 1.28
Chen *et al*[74], 2019, China	Low Socioeconomic S.[1] 0.31	Reproduction techniques[1] 5.63	
	Unemployment[1] 2.24	Lack of knowledge about prenatal health[1] 1.43	
	Marital dissatisfaction[1] 4.46		
	Living with extended family[1] 2.52		
	Live in a rural area[1] 1.71		
Hu *et al*[75], 2019, China	Younger age[1] 0.93		
	Low Educational L.[1] 1.29		
	Unemployment[1] 1.075		
	Marital dissatisfaction[1] 4.77		
Marcos-Nájera *et al*[49], 2020, Spain	Marital dissatisfaction		Lack of self-esteem
			Low social support

[1]Odds ratio of predictor variables; (*P* value). Low Educational L.: Low Educational Level; Low Socioeconomic S.: Low Socioeconomic Status; U. pregnancy: Unplanned pregnancy.

Although the age of a woman is a variable considered in all the studies, it is not always analyzed in relation to the presence of depression in pregnancy. In this regard, the results provided by the studies are inconsistent. Several studies have indicated that younger maternal age increases the likelihood of depression during pregnancy[28-32]. Thus, age younger than 25[12], younger than 20[23], or between 15-20-years-old[33]

have been associated with increased risk of antenatal depression. This may be because younger women tend to have a more unfavorable and unstable economic position. Likewise, younger age may be associated with lower educational attainment and income level, lower paying jobs, or unemployment[33]. On the contrary, other studies have found that older maternal age has been associated with higher risk of antenatal depression. Specifically, it was found that age older than 35[24] and older than 30-years-old[34] were associated with increased risk of depression. Accordingly, rather than age *per se*, the explanation behind these inconsistencies may be more related to cultural issues, such as the fact that in some societies being a young mother is the norm and expected, while in others the opposite is true. Also, the personal baggage that older women bring to motherhood with regard to potential difficulties in conceiving along with anxiety about obstetric and pregnancy complications associated with advanced maternal age[35,36] could be a possible explanation for their higher prevalence of depression.

Regarding educational level, there seems to be a consensus among researchers as when an association has been found, it has always been between lower educational level and antenatal depression[24,33,37-39]. It should be noted, though, that a low level of education is often related to other socioeconomic disadvantages, such as low income[24]. Thus, it can also be explained by the fact that these women present low self-esteem and self-efficacy[40,41], as they may feel inferior both socially and because of their inability to access better paid jobs.

Another factor that has been studied in relation to depression during pregnancy is socioeconomic status. In this case, different studies also agree that being in an unfavorable socioeconomic situation is associated with the presence of antenatal depression[11,34,42-44]. It has been proposed that during the perinatal period women with low socioeconomic status may fear being unable to care for their children[45]. Similarly, low socioeconomic status is often followed by increased stress related to economic hardship, which in turn is a risk factor for antenatal depression[46].

One factor related to socioeconomic status is the employment status of both the woman and her partner. In this regard of not having a paid job, the woman[12,23,47] and/or the partner[38], has been associated with the presence of antenatal depression. In the same vein, being a homemaker has also been associated with antenatal depression[12]. A possible explanation could be the fact that not working and/or being a homemaker implies having a smaller social support network and a certain isolation[47]. Likewise, being a homemaker may be an indicator of low educational level and lower economic resources[12]. It is worth noting that studies such as that of Husain *et al*[38] in Iran did not find such a relationship, but they did find a connection with the fact that it is the partner who is unemployed. Cultural issues related to the role of women in the world of work may be the background of this association. Another aspect that could explain this association could be women's frustrations at the fact that pregnancy did not allow them equal access to the labor market.

Another factor associated with depression in pregnancy is related to marital status. Being single, not cohabiting with a partner, not having a stable partner or with a certain level of commitment[11,25,33,34,42], and/or cohabiting as a domestic partner [23] has been associated with increased risk of antenatal depression. The absence of a partner may mean less social support[15,24] or lead to a worse economic situation, and it is sometimes associated with unintended pregnancy[33].

On the other hand, maintaining an unsatisfactory relationship with a partner has been associated with increased risk of depression during pregnancy[46-50]. One possible explanation for this relationship is based on the fact that physiological and psychological changes that occur during pregnancy often influence women's moods, and they seek support from their partner. Consequently, the lack of such support may increase the likelihood of prenatal depression. Indeed, difficult or strained couple relationships marked by disharmony increase rates of prenatal depression[21,51]. Similarly, partners of women who have a depressive episode report greater marital distress. Likewise, these couples tend to resort to less constructive tactics to resolve their conflicts[51]. In the same way, being a victim of gender-based violence has also been associated with increased risk of antenatal depression[26,33,43].

The context of belonging of the pregnant woman as well as the social environment in which she lives and socializes are also factors that may be related to the risk of suffering depression. Thus, not being of the same race as the country in which one lives and/or being a foreigner[15,25,47] along with social isolation[23] have been described as variables associated with depression in pregnancy. The explanation behind all these situations is the lack of social support.

Obstetric variables

It is increasingly common for researchers to consider obstetric and/or pregnancy-related factors when looking for variables associated with antenatal depression. Pregnancy planning is one of the most studied variables, having been found by several studies that the situation of unplanned pregnancy is a risk factor for antenatal depression[11,34,46-48,52]. An unplanned or unwanted pregnancy carries an enormous emotional burden. Moreover, these women may not be financially, psychologically, or socially prepared to cope with the demands of pregnancy[53]. That is, they may have difficulty reconciling maternal needs and other responsibilities at home or at work. Another explanation may be the fact that these women tend to have more unstable psychosocial environments and feel a lack of security and attachment with their partner[54]. In addition, couples with unplanned pregnancies tend to have more marital conflicts[55], which in turn increases the risk of antenatal depression.

Regarding parity, there are contradictory results. While one study has found nulliparity was associated with increased risk of antenatal depression[50], most studies have found that being multiparous has been associated with increased risk of antenatal depression[6,10,12,24-26,52]. One possible explanation is that the caregiving and parenting-related stress experienced by these women (*e.g.*, expectations of coping with the new child) may make them more vulnerable to depression[24].

Variables related to the woman's previous and current obstetric history have also been studied in relation to antenatal depression. Thus, the existence of previous abortions[6,34,37,52], complications in previous delivery and/or pregnancy as well as those that may exist in the course of the current gestation[6,33,38], and a history of caesarean section[33,56] have been associated with increased risk of depression during pregnancy. These events are very stressful during pregnancy[21]. As a matter of fact, women who have had a previous surgical delivery are more likely to experience feelings of loss, personal failure, and low self-esteem[33].

Additionally, the presence of physical symptoms, such as nausea, vomiting, and fatigue, have been associated with increased risk of antenatal depression because they can have negative effects on women's daily lives[39]. With respect to caesarean section, this sort of delivery is highly influenced by cultural issues too. In some countries, having a caesarean birth would be an adverse event, while in others the adverse event is having a normal delivery. In fact, in recent decades, caesarean deliveries have become normalized in many countries, up to the point that organizations such as the World Health Organization have warned of the risks that these entail. It is worth highlighting the aspect of "perception" here because in many cases what the woman considers a complication is not so from the clinical point of view. For instance, some women perceive that having low back pain or nausea are complications, while for a health professional both entities would be considered physiological or within normality. Therefore, what it is relevant at a psychological level is not what is reflected in the medical history or what the professional thinks, but the perception that the woman has of her own process.

Psychological variables

The psychological variables that have been most closely related to antenatal depression will be discussed below. Notable among these variables are a history of depression, anxiety, stress, and low perception of social support.

History of depression: Family and personal history of psychological disorder, specifically, personal history of depression[10-12,24,26,44], or psychological disorders in general[47] as well as family history of depression[48] have been associated with an increased risk of antenatal depression. Specifically, it was found that women with a previous history of depression had a tenfold increased risk of antenatal depression [26]. Patton *et al*[57] followed a sample of women for more than 30 years and found that 85.0% of those who had depressive symptoms during pregnancy also had mental health problems during adolescence or adulthood. This association may be due to the existence of a vulnerability to depression that may be intensified by lifestyle changes (sleep and eating patterns) as well as physical changes (symptoms and limitations) that take place in pregnancy[24]. Another possible reason that could explain this fact is the interruption of depression pharmacological treatment by the mother at the beginning of pregnancy for fear of possible teratogenic effects for the foetus[5].

Anxiety and stress: Regarding anxiety, its presence before and/or during pregnancy has been found to be associated with antenatal depression[10,15,46,50,56]. This may be due to the frequent comorbidity of both disorders[56]. In addition, both anxiety and antenatal depression share risk factors[58]. Ross *et al*[59] concluded that more than

50.0% of pregnant women with depression had also been diagnosed with anxiety. Therefore, depressive and anxiety disorders during pregnancy are probably not independent clinical entities[60]. It is worth noting that the Edinburgh Postnatal Depression Scale, designed specifically to detect depressive symptomatology, includes three items that assess anxiety, so it is not surprising that women who score high on this scale score high on depression and on anxiety.

Likewise, different studies have found that high levels of perceived stress during pregnancy and adverse life events play an important role in the onset of antenatal depression[15,42,46,50,61-63]. This may be because the time of pregnancy is especially considered as stressful for many women because of the changes this period causes in their lives[64]. They may experience fear for the baby's health and well-being, fear of impending childbirth, hospitals, postpartum, and maternal role coping[65]. In fact, maternal stress, also called pregnancy-specific distress or pregnancy-related stress[66], is considered a negative emotional state different from depression and anxiety[67].

Social support: Regarding social support, research agrees that the absence or low perception of social support[39,46,49] and specifically the lack of partner support[43, 52] increases the risk of antenatal depression. Social support has been found to be crucial for psychological well-being during pregnancy[39]. In this regard, family contexts are important, although they differ substantially across cultures[52]. On the one hand, nuclear family settings are common in Western countries, whereas extended family structures are more frequent elsewhere such as Asia and/or Arab countries [18]. Some authors[38,68] found that women living in a nuclear family environment were at higher risk of developing antenatal depression *vs* those in the context of a multigenerational household. This may be due to women feeling isolated and less socially supported than they would in a larger family setting. In contrast, living in an extended family has been identified as a protective factor for antenatal depression[69]. However, González-Mesa *et al*[52] found the opposite scenery, as women living in larger families, with a larger number of children and more relatives living in the same household, were at higher risk for antenatal depression. Despite beliefs about the strength of traditional family relationships, 40.0% of these women claimed to have had insufficient family support. Perhaps in the case of social support it is not so much the number of people you live with, but rather the support they give you.

In this respect, the possible explanations provided in the studies, for the connection between lower perception of social support and depression, are more based on the protective effect of social support on depression than on low social support as a risk factor for depression. Moreover, social support during times of stress can be a protective factor against the onset of depression, as it moderates the stress of pregnancy and childbirth and increases maternal self-efficacy[70], that is, the belief in one's own capacity as a mother. Therefore, continuous social support can facilitate the process of adaptation to motherhood[71]. However, it should be noted that the important thing is that the woman perceives that she is indeed receiving this support.

Limitations

This review has met some limitations that ought to be mentioned. First, the review is confined to studies published in English, and thus generalizability of the findings is limited. Second, we did not conduct a meta-analysis of the findings, which may have added additional information about the differential impact of each risk factor. Nevertheless, most of the risk factors described in this review have been independently replicated by a number of studies. This review has excluded research prior to 2010 and based on high-risk populations (*e.g.*, studies conducted in women with pre-existing diseases, residents of war zones, poverty conditions, victims of gender-based violence). Therefore, the generalizability of the findings to these populations may be limited.

CONCLUSION

In view of the results found in this review, there seems to be evidence that sociodemographic, obstetric, and psychological factors can influence the mental health of pregnant women. Many of these factors cannot be modified, such as age and obstetric and psychological history, but others, such as anxiety, stress, or lack of social support, can be influenced through appropriate interventions. Therefore, it is important to identify these risk factors from the first pregnancy follow-up visits in order to be able to carry out preventive and/or therapeutic interventions if necessary. For this purpose,

we consider it necessary to implement routine and protocolized screening tools to identify women at risk of depression in regular pregnancy check-ups. Likewise, better use could be made of health resources already available as is the case of maternal education classes. The mere fact of attending, of being in contact with other women in the same situation and with the same needs, and of having a professional of reference who listens empathetically and resolves doubts can minimize the impact of the possible fears and worries that most women have during pregnancy. Both strategies would prevent and/or reduce the psychological distress of pregnant women, limit its continuation in the postpartum period, and, therefore, reduce the costs of care for the depression. By intervening at the right time, future problems can be prevented.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 337-346

DOI: 10.5498/wjp.v11.i7.337

ISSN 2220-3206 (online)

MINIREVIEWS

Psychological and mental health impacts of COVID-19 pandemic on healthcare workers in China: A review

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Author contributions: Cai CZ drafted the manuscript; Lin YL, Hu ZJ, and Wong LP reviewed and finalized the manuscript; all authors have read and approved the final manuscript.

Supported by the Pilot Project of the Fujian Provincial Department of Science and Technology, No. 2020Y0005.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

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Abstract

The coronavirus disease-19 (COVID-19) pandemic has put healthcare workers in an unprecedented situation, increasing their psychological and mental health distress. Much research has focused on the issues surrounding anxiety, depression, and stress among healthcare workers. The consequences of mental health problems on healthcare workers' physical health, health-compromising behaviours, suicide ideation, family relationships, and job satisfaction during the COVID-19 pandemic are not well studied. Enhanced psychological stress has known effects on an individual's physical health. In healthcare workers with pre-existing comorbidities, psychological stressors may exacerbate their current health problems. Healthcare professionals are known to have a high risk of substance use, hence they may be at risk of development of substance use addiction or vulnerable to addiction relapse. Frontline COVID-19 healthcare workers are being pushed above and beyond their limits, possibly resulting in suicidal tendencies. Furthermore, the burden of high workload and burnout may also have serious manifestations in relationships with family and an intention to quit their jobs. Future studies should explore the above-mentioned deleterious consequences to provide insight into the development of mental healthcare strategies to combat the psychological impact of COVID-19 on healthcare workers during the COVID-19 emergency. It is imperative to employ strategies to care for and policies to protect the psychological well-being of healthcare workers.

Key Words: Psychological; Mental health; COVID-19; Healthcare workers; China

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Manuscript source: Invited manuscript

Specialty type: Behavioral sciences

Country/Territory of origin: Malaysia

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 8, 2021
Peer-review started: February 8, 2021
First decision: May 5, 2021
Revised: May 13, 2021
Accepted: June 23, 2021
Article in press: June 23, 2021
Published online: July 19, 2021

P-Reviewer: Li BF
S-Editor: Zhang H
L-Editor: Wang TQ
P-Editor: Ma YJ

Core Tip: Much has been investigated surrounding the issue of anxiety, depression, and stress during the coronavirus disease-19 (COVID-19) pandemic among the healthcare workers in China. Nonetheless, the consequences of psychological and mental distress on healthcare workers' physical health, general well-being, family relationships, job satisfaction, and anticipated turnover are not well studied. We herein discuss the multi-faceted consequences of psychological and mental health on healthcare workers in China during the COVID-19 pandemic. This review also highlights the important areas overlooked in research and mental health policies.

Citation: Cai CZ, Lin YL, Hu ZJ, Wong LP. Psychological and mental health impacts of COVID-19 pandemic on healthcare workers in China: A review. *World J Psychiatr* 2021; 11(7): 337-346
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/337.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.337

INTRODUCTION

Coronavirus disease-19 (COVID-19) infection was first reported in Wuhan, China in December 2019, and spread rapidly throughout China. Just 3 mo later, the World Health Organization (WHO) declared the spread of the COVID-19 as a pandemic. In a short one year, the COVID-19 pandemic has become a major global health crisis. While the pandemic is still a crisis in many countries worldwide, China has managed to control the pandemic rapidly and effectively in just over 3 mo after its onset[1]. As of the end of December 2020, China had confirmed 96324 cases of COVID-19 and 4777 deaths, while there have been over 79.2 million cases and over 1.7 million deaths globally since the start of the pandemic[2].

The COVID-19 pandemic is not only a threat to human life. Beyond the direct impacts of the virus, the mental health of the entire population is profoundly impacted. More importantly, the psychological and mental health of healthcare workers has been greatly challenged during this pandemic owing to their often extensive and close contact with COVID-19 patients in healthcare settings. High rates of infections and deaths among the healthcare workers involved in the fight against COVID-19 are causing them to experience high levels of distress and fear[3,4]. Worldwide, COVID-19 has affected large numbers of frontline healthcare workers. As of April 8, 2020, the WHO estimated that over 20000 health workers in 52 countries had contracted COVID-19[5]. In China, the outbreak has forced health professionals to work under extreme pressure and uncertainty, battling the novel coronavirus that is not fully understood and has claimed many lives. In a short intense 3 mo of battle against the coronavirus, the outbreak has exerted significant negative psychological impacts on healthcare professionals, particularly frontline health workers. A study of over 72000 patients with COVID-19 by the Chinese Centre for Disease Control and Prevention showed that around 3000 healthcare workers had become infected by February, accounting for 3.8% of all cases of COVID-19[6]. In addition to the fear of contagion during the early phase of the outbreak, healthcare workers in Wuhan also faced enormous pressure, including inadequate protection from contamination, work burden, isolation, witnessing patients suffering and dying, a lack of contact with their families, fear of transmitting the disease to families and loved ones, and exhaustion, which collectively contributed to serious mental health problems such as stress, anxiety, depressive symptoms, and insomnia[4,7].

Since the onset of the pandemic, there have been many published studies on the mental health of healthcare workers in the COVID-19 pandemic in China and other countries impacted by the COVID-19 pandemic. There were also several systematic reviews and meta-analyses that synthesised the findings of all published studies. A systematic review and meta-analysis of 13 studies of mental health during the COVID-19 pandemic published up to April 17, 2020, of which 12 were from China and one from Singapore, reported a pooled prevalence of 23.2% for anxiety, 22.8% for depression, and 38.9% for insomnia[8]. An integrative review of the mental health of healthcare professionals in China during the new coronavirus pandemic found intense psychological experiences, traumatization, and various mental health disorders among healthcare workers, while also describing the importance of self-coping and psycho-

logical needs[9]. A recently published meta-analysis of eight studies of frontline healthcare workers in China reported that the pooled prevalence of depression and anxiety was 31.5% and 23.7%, respectively[10], which was relatively higher than the former.

Although much has been investigated surrounding the issue of psychological and mental health impacts of the COVID-19 pandemic, most of the current published literature and reviews have investigated the level of anxiety, depression, and stress. The negative consequences of psychological and mental impacts during the era of the COVID-19 pandemic remain a relatively neglected area of inquiry. Among these are physical health, health-compromising behaviours, such as substance use disorders, suicide attempts or suicidal ideation, the disruption of family relationships, and the intention to leave jobs. To date, it has been over a year since COVID-19 first emerged in China. Many countries in the world are facing a resurgence of COVID-19 cases as the pandemic progresses. Healthcare workers in China may once again resume the COVID-19 battlefield and continue facing psychological distress. In light of the preceding discussion, this article discusses the multi-faceted consequences of psychological and mental health on healthcare workers in China during the COVID-19 pandemic.

PHYSICAL HEALTH

Recent research continues to demonstrate that poor mental health is related to adverse physical health[11]. Mounting evidence is showing associations between psychological distress and physical health such as hypertension and cardiovascular diseases[12]. Emerging evidence indicates that the COVID-19 pandemic has posed significant psychological stress on the community with emerging cardiovascular implications [13]. Recent reports show the link between emotional pressure caused by COVID-19 and takotsubo cardiomyopathy presenting as acute heart failure[14]. Despite this, increasing trends in the prevalence of chronic diseases are not prominent. This could be due to a large delay in treatment-seeking during the pandemic[13]. Henceforth, public as well as healthcare workers with pre-existing cardiovascular comorbidities and psychological stressors may exacerbate their current health conditions. More importantly, a study in China showed that patients with hypertension were associated with severe outcomes from COVID-19[15]. Furthermore, there is also a significant association between the fatality rate in COVID-19 patients and cardiovascular metabolic diseases[16]. As in many developing countries, in China, hypertension remains a pervasive problem among Chinese adults. Results from the China Hypertension Survey 2012–2015 stated that 23.2% (approximately 244.5 million) of the Chinese adult population ≥ 18 years of age had hypertension[17]. The high prevalence of cardiovascular risk factors was also reported among healthcare workers in China and is of growing concern. The prevalence of hypertension among nurses in China was reported to be close to 30%[18]. Although it is well established that stressful life events are a factor mediating the progression of chronic diseases such as cancer growth and development of metastases[19], as well as metabolic syndrome and type II diabetes mellitus[20], direct evidence linking to COVID-19 pandemic related stress has yet been reported. Considering that untreated psychological and mental health problems may cause severe physical health problems, it is of utmost importance not to downplay the psychological and mental health of healthcare workers with cardiovascular risk factors or chronic illnesses during their fight against COVID-19.

Thus, it is essential to build a work environment where there is some recognition of mental health as a dangerous risk factor to physical health, particularly during the current pandemic situation. Raising awareness of mental health as a dangerous risk factor to physical health is also important because mental health literacy may help an individual to cope, seek help, or self-advocate for health improvement[21]. Having a workplace mental health policy that looks into the well-being of healthcare staff with health issues or comorbidities is of paramount importance. Local evidence on the interlink of physical and mental health problems remains a crucial area of investigation in China.

SUBSTANCE USE DISORDERS

The COVID-19 pandemic has serious implications for people with substance use disorders. Fear of contagion, uncertainty and anxiety, social distancing and isolation, loneliness, and economic repercussions were among the factors that promote substance use during the pandemic[22]. Deaths from alcohol, drugs, and suicide, collectively known as "deaths of despair", are receiving growing international attention[23,34]. According to the findings of a study from the Well Being Trust released in May 2020, an estimate of 75000 "deaths of despair" associated with drug, alcohol, and suicide has been directly related to the COVID-19 pandemic[25]. Recently, it is estimated that the number of "deaths of despair" could double up to 150000 due to the pandemic's slow recovery[26]. Stressful events have long been known to also cause increased substance use risk in healthcare workers[27-29]. An issue that is overlooked in the COVID-19 pandemic crisis among healthcare workers is the reactive behaviour to negative impacts of disasters such as the development of addiction and addiction relapse vulnerability. There has been a report of an increase in substance use among people who have existing substance problems in China in the era of the COVID-19 pandemic[30]. Nevertheless, to date, relatively little has been reported in substance use among healthcare workers in China during the COVID-19 pandemic. Healthcare workers may similarly be vulnerable to substance use disorders during the COVID-19 pandemic. In a previous report, post-traumatic stress disorder (PTSD) and alcohol abuse or dependence symptoms 3 years post Beijing's 2003 SARS outbreak were prevalent among hospital employees who lived through the outbreak[31]. Substance use prevention and cessation support should be provided in healthcare settings. Increased substance abuse during the COVID-19 pandemic among people without a substance abuse history has not been reported and warrants further observation. Despite this, psychological intervention and advice for preventing substance use during the COVID-19 pandemic should be disseminated to the public at large and specifically targeted at people with a history of substance abuse. Given the amount of intensified psychological and mental issues facing medical care workers during the pandemic, understanding the extent and nature of healthcare workers' substance use disorders is essential for appropriate psychosocial management and successful treatment. However, the stigma associated with substance use disorders covers the entire trajectory of diagnosis, prevention, treatment, and recovery; hence, this is a major obstacle for healthcare-providers seeking diagnosis and treatment. There is a need to sensitise the public and healthcare organisations about addiction-related issues among healthcare workers during this pandemic. Family members' awareness and involvement in the treatment of substance use disorders are imperative[32]. Health systems should also facilitate access to substance use disorder treatment for healthcare workers, particularly those with pre-existing psychiatric conditions.

SUICIDE ATTEMPTS AND SUICIDAL IDEATION

Suicide is a worldwide phenomenon and studies have shown that suicide deaths are related to mental health disorders. There is growing concern that multiple lines of evidence point towards the increase in the rates of suicide attempts and completed suicides during the COVID-19 pandemic[22,32-35]. The profound pandemic related psychological impacts associated with prolonged social isolation, loneliness, fear of COVID-19 infection, uncertainty, occupational deprivation, and economic difficulties lead to the development or exacerbation of depression and anxiety, and ultimately aggravate vulnerability to suicidal thoughts and behaviours[22]. Vulnerable populations to the exacerbation of psychological or mental-related disorders and suicidal thoughts include individuals with pre-existing psychiatric disorders, less resilient people, those living in high COVID-19 prevalence areas, and people who have lost loved ones to COVID-19[36,37]. People in the medical-related profession have also been known to have a high prevalence of suicide attempts and suicidal ideation[38]. It was noted that the COVID-19 pandemic has increased the risk of suicide among healthcare workers due to the increased psychological distress, including witnessing COVID-19 patients' deaths, a lack of feelings of control, personal blame for the inability to do more for patients, and increased working hours[39]. Suicide cases among healthcare workers have been reported across many countries including the United States, England, Italy, Mexico, and India[40-42].

In China, relatively little has been reported on suicidal ideation or suicide attempts among the healthcare workers in Wuhan, the epicentre of the coronavirus outbreak,

despite a high level of psychological and mental disorders during the early phase of the outbreak. China has promptly launched a psychological intervention and mental health support system to cope with the widespread psychological stress during the COVID-19 pandemic[43,44]. Psychological assistance hotlines providing online psychological counselling services have been established by mental health professionals in medical institutions, universities, and academic societies throughout all provinces and regions in mainland China, which provide free 24-h services that were widely made available to the public and healthcare workers. The online psychological self-help intervention systems include online cognitive behavioural therapy for depression, anxiety, and insomnia[45]. Of note, the current literature is lacking on suicide attempts or suicidal ideation in healthcare workers in China. It is unclear whether the lack of evidence is due to under-reporting or under-diagnosis. It is well known that despite the high rates of depressive and anxiety disorders among physicians, dealing with suicide is challenging as stigma and embarrassment prevent a large number of them from seeking care for mental health diagnosis and treatment[46].

Although the COVID-19 pandemic is largely under control in China now, PSTD in the aftermath of the COVID-19 pandemic is an issue that should not be overlooked. The impact on mental health can be long-lasting for large-scale crisis events like the COVID-19 pandemic[47]. The distressing events of the past 3 mo, particularly among the frontline healthcare workers providing care to patients with COVID-19, witnessing the pandemic's massive death and trauma, could lead to long-term mental health problems. A study reported that a total of 3.8% of 377 healthcare workers in China reported PTSD a month after the outbreak and those with PTSD had a significantly higher probability of experiencing poor sleep quality[48]. Another study of 863 medical care workers from seven provinces in China reported that 40.2% were positive for PTSD[49]. PTSD is known to be a risk factor for suicide and was found to account for 0.6% of suicides in men and 3.5% in women[50]. The psychological sequelae of the pandemic will probably persist for months and years to come and suicide is probably going to become an even more significant concern as the pandemic unfolds[35]. Suicide prevention research emphasises that building meaningful social connections and interventions to decrease burdensomeness among healthcare workers are urgently needed.

FAMILY RELATIONSHIP AND WELL-BEING

The coronavirus pandemic has profound negative emotional impacts affecting personal and family harmony worldwide. The fear and uncertainty associated with pandemics provide an enabling environment that may aggravate family conflicts or violence in a family or relationship[51-53]. Prolonged lockdown and long-term home isolation measures and the stress of the COVID-19 pandemic have aggravated family conflicts and strained relationships, leading to a variety of family problems, including family violence and divorce. In China, after the 2-mo lockdown, the number of cases of family violence and divorces surged in March[51]. It is unclear if the strain of life under lockdown has contributed to the increase in divorce rate as the unprecedented number of divorces could also be due to backlog in cases as the pandemic has forced offices to close for months. Little is known about whether the adverse psychological or mental health of healthcare workers during the COVID-19 pandemic has negative effects on their families or personal lives. It is well established that the high workload of healthcare workers has restricted their family life, leading to burnout and distress, which consequently have serious manifestations on family relationships and marital complications[54,55].

More research is needed to assess the experience of family turbulence due to the COVID-19 pandemic among healthcare workers in China. Sudden changes in daily work lives during the pandemic and high exposure to psychological distress are situations that put healthcare providers at an increased risk of negative effects on family relationships. Policies should take into consideration the implications of the pandemic on the family members of healthcare providers. Current mental health services and interventions for healthcare providers should adopt a more holistic approach, including supportive care for their family members and loved ones.

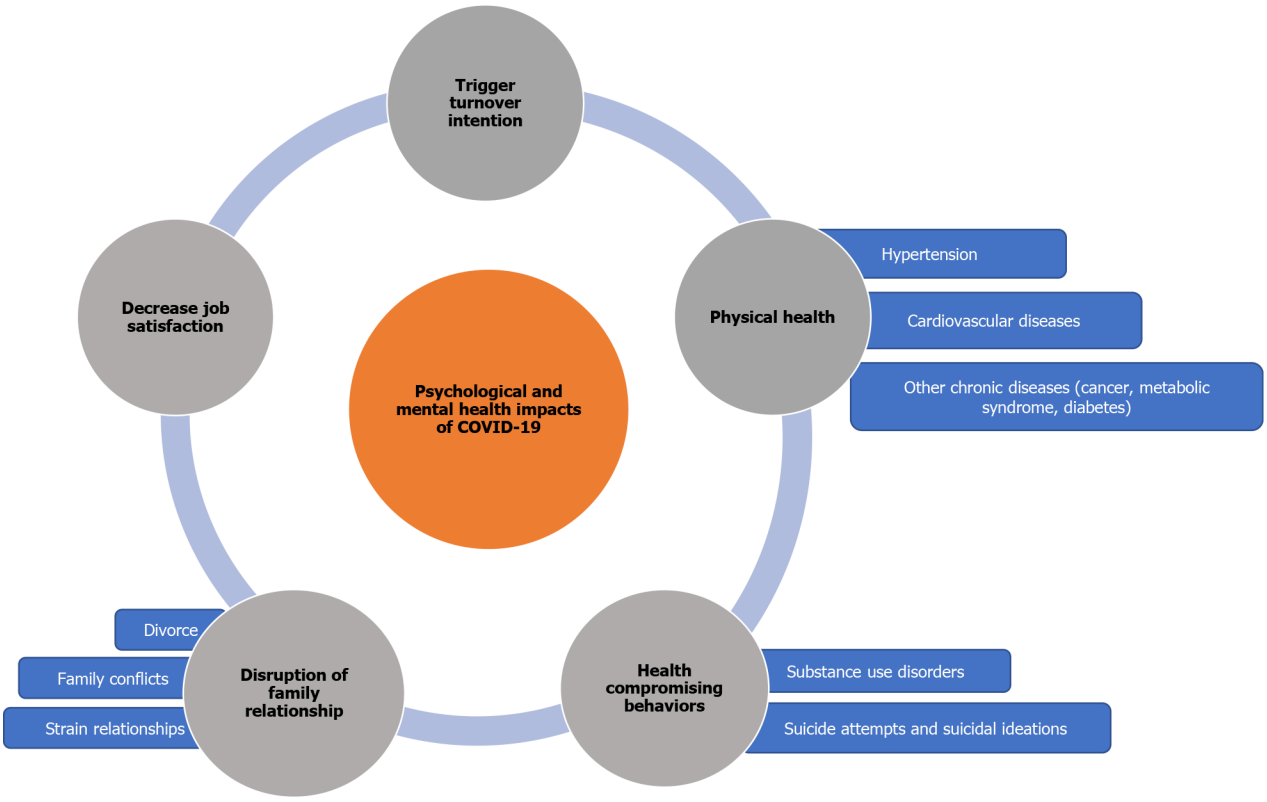


Figure 1 Summary of the psychological and mental health impact of coronavirus disease-19 pandemic. COVID-19: Coronavirus disease-19.

JOB SATISFACTION AND TURNOVER INTENTION

As the pandemic progressed, evidence began to show a deterioration in the psychological and mental well-being of healthcare workers, resulting in decreased job satisfaction and triggering turnover intention[56,57]. In China, although the statistics of healthcare workers quitting their jobs during the COVID-19 pandemic are unknown, poor psychological well-being and heightened turnover intention were evident in healthcare workers fighting COVID-19 during the peak of the outbreak[58,59]. It is crucial for healthcare workers to feel satisfied with their jobs during the COVID-19 pandemic. Poor level job satisfaction among healthcare workers during the COVID-19 pandemic has been reported in several studies worldwide. Mean occupational satisfaction of 3.6 (score range, 1-5) was reported during the COVID-19 pandemic among Israeli nurses[60]. Job satisfaction score of 2.8 (out of a possible score of 4) was reported in a large-scale study among healthcare workers in Italy[61]. Large-scale empirical study assessing the level of job satisfaction of healthcare workers in China is lacking. To date, two small-scale studies reported a job satisfaction score of 32 (out of possible 48)[59] and 82 (out of possible 100)[62] in healthcare workers in China during the COVID-19 pandemic. Further large-scale studies are warranted to accurately determine the level of job satisfaction of healthcare workers in China in the era of the COVID-19 pandemic. The shortage of healthcare professionals in China is an issue that has long been at the forefront of the healthcare industry before the COVID-19 pandemic, and the COVID-19 pandemic has simply increased the demand for healthcare professionals in China, resulting in the heightened importance of preventing the loss of the medical workforce in the healthcare service[63]. It is important to identify specific psychological or work problems surrounding poor job satisfaction and turnover intention among healthcare workers to enable more accurate targeted interventions. The catastrophic toll on mental health, inadequate protection, and fear of safety, along with that of their families, may cause many healthcare workers to choose to step away from their jobs[58]. As the need for medical doctors continues to increase with the world facing the unprecedented global health threat of coronavirus infection, the government must do everything in its power to retain employees in the healthcare setting.

The summary of psychological and mental health impacts of COVID-19 pandemic discussed is illustrated in Figure 1.

CONCLUSION

There is a need to recognise the adverse consequences of psychological and mental health problems on the well-being of healthcare workers. Poor psychological and mental health among healthcare workers is harmful not only to themselves, but also to their patients, families, organisations, and healthcare services. The public, healthcare organisations, and government authorities should be made aware of the manifestations of mental health among healthcare workers, their correlations, and the fact that any strategies to manage them must encompass all levels of society. The lacunae in the existing literature on the consequences of psychological and mental problems on healthcare workers may need to be completed over time through further research. Psychiatry and psychological first aid should be considered broadly during a crisis such as the COVID-19 pandemic. Efforts to destigmatise help-seeking behaviour for psychological and mental health problems are warranted. A workplace mental health strategy and policy are essential for a healthy workplace environment during a pandemic crisis.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 347-354

DOI: 10.5498/wjp.v11.i7.347

ISSN 2220-3206 (online)

MINIREVIEWS

Impact of SARS-CoV-2 on neuropsychiatric disorders

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Author contributions: All authors listed made a substantial, direct and intellectual contribution to the work, and approved it for publication. Robinson-Agramonte MA organized and planned the manuscript; Robinson-Agramonte MA, Prendes N and Noris E wrote the paper; Siniscalco D drafted and revised the manuscript; Goncalves CA and García García critically revised the manuscript; Brigida AL searched and provided the references, Schultz S edited and corrected the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Abstract

Evolving data show a variable expression of clinical neurological manifestations in patients suffering with coronavirus disease 2019 (COVID-19) from early disease onset. The most frequent symptoms and signs are fatigue, dizziness, impaired consciousness, ageusia, anosmia, radicular pain, and headache, as well as others. Based on the high number of series of cases reported, there is evidence for the implication of the immune system in the pathological mechanism of COVID-19. Although the exact role of the immunological mechanism is not elucidated, two main mechanisms are suggested which implicate the direct effect of severe acute respiratory syndrome coronavirus 2 infection in the central nervous system and neuroinflammation. In the context of neurological manifestations associated with COVID-19, neuropsychiatric disorders show an exacerbation and are described by symptoms and signs such as depression, anxiety, mood alterations, psychosis,

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Cuba

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 11, 2021
Peer-review started: February 11, 2021
First decision: March 16, 2021
Revised: March 18, 2021
Accepted: May 24, 2021
Article in press: May 24, 2021
Published online: July 19, 2021

P-Reviewer: Morenikeji OB
S-Editor: Liu M
L-Editor: Webster JR
P-Editor: Li JH

post-traumatic stress disorder, delirium, and cognitive impairment, which appear to be common in COVID-19 survivors. A worsened score on psychopathological measures is seen in those with a history of psychiatric comorbidities. We review the neuropsychiatric manifestations associated with COVID-19 and some critical aspects of the innate and adaptive immune system involved in mental health disorders occurring in COVID-19.

Key Words: COVID-19; Immunological mechanism; Neuropsychiatric manifestation; Cytokine storm; Adaptive immune response; Innate immune response

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Core Tip: Severe acute respiratory syndrome coronavirus 2 infects the central nervous system and drives neuroinflammation. In coronavirus disease 2019 (COVID-19) patients, neuropsychiatric disorders are showing an exacerbation and are described by symptoms and signs such as depression, anxiety, mood alterations, psychosis, post-traumatic stress disorder, delirium, and cognitive impairments. Some critical aspects of the innate and adaptive immune system are also involved in mental health disorders occurring in COVID-19.

Citation: Robinson-Agramonte MA, Gonçalves CA, Noris-García E, Préndes Rivero N, Brigida AL, Schultz S, Siniscalco D, García García RJ. Impact of SARS-CoV-2 on neuropsychiatric disorders. *World J Psychiatr* 2021; 11(7): 347-354
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/347.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.347

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic, at the time of this publication, has shown a tendency to a reduction in contagiousness globally; however, the fire has not gone out. Reports of the World Health Organization and Johns Hopkins University confirm as of March 18, 2021 that there have been 121 214 686 cases diagnosed around the world and 2 680 740 deaths as consequence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is accepted that this infection affects the nervous system in various ways as the virus is deeply neurotropic and neuroinvasive [1]. It will be necessary to understand the post-infectious manifestations of COVID-19 to guide long-term management of neurodevelopmental and neuropsychiatric diseases.

Data derived from published clinical papers and case reports indicate that the main clinical manifestations of COVID-19 include anosmia, ageusia, central respiratory failure, stroke, acute inflammatory demyelinating polyneuropathy, toxic metabolic encephalopathy, headache, myalgia, myelitis, ataxia, and others[2,3]. As suggested earlier, in the acute phase, COVID-19 is a potential causal factor of neuropsychiatric manifestations, such as encephalopathy, psychosis, insomnia, and mood changes[4].

The neuropsychiatric manifestations of both viral infection *per se* and secondary to the host neuroinflammatory reaction are attributed to: (1) Microglial activation[5,6]; (2) An imbalance of central neurotransmitters, such as noradrenaline, epinephrine, and serotonin (with potential implication in neuropsychiatric disorders); and (3) A disruption of the blood–brain barrier (BBB) leading to peripheral immune cell transmigration into the central nervous system (CNS)[7]. This manuscript reviews core critical aspects of neuropsychiatric disorders and COVID-19 while focusing on the immunopathology and related clinical symptoms.

POTENTIAL IMMUNE MECHANISM AND NEUROPSYCHIATRIC SYMPTOMS IN COVID-19

The neuroinvasive potential of coronavirus has been reported in SARS-CoV-1 patients

and experimental animals[6], and it was also speculated to include SARS-CoV-2 in relation to the routes and mechanisms of CoV neurotropism[8,9]. Potential mechanisms of neuropsychiatric manifestations in COVID-19 are discussed from different viewpoints[10-13]; however, we will focus this short review on two main core mechanisms in support of CNS involvement in mental health associated with COVID-19: Direct viral infiltration into the CNS and neuroinflammation with related neuropsychiatric manifestations (Figure 1).

DIRECT VIRAL INFILTRATION INTO THE CNS

It is well-known that viral infection takes place by recognition and binding of SARS-CoV-2 virus-host receptor, specifically angiotensin-converting enzyme 2 (ACE-2), which is expressed in multiple tissues within the human body, including the CNS[1]. In the CNS, infection has been identified in glial cells and endothelial cells of blood vessels in the brain. In brain blood vessels, it has been demonstrated that it can induce disruption of the BBB and increase permeability[14-16].

One pathway for CoV invading the CNS is through synaptic routes of nerve cells, which seems to infect CNS retrograde *via* peripheral sensory nerves[17]. On the other hand, the olfactory nerve cells seem to be a feasible route for direct CNS infection, facilitated by the ACE-2 receptor expressed in olfactory epithelial cells[1]. Although this mechanism does not have a full consensus from various research groups, several pieces of evidence confirm that after cell infection by CoVs, death can be caused by autophagy, apoptosis, pyroptosis, or by elimination *via* innate immune cells[17,18] (Figure 1).

NEUROINFLAMMATION

It has been found that following SARS-CoV-2 infection, activation of both the innate and adaptive arms of the immune system are induced toward an uncontrolled systemic response with the intervention of a non-specific immune mechanism involving activated macrophages, neutrophils, and natural killer cells, as well as an adaptive immune mechanism with a relevant effector function mediated by dendritic cells and lymphocytes. The adaptive mechanism includes T helper cells (CD4), T cytotoxic cells (CD8) and B cells, which is followed by exaggerated pro-inflammatory cytokine release from these effector cells, such as interleukin (IL)-1b, IL-6, IL-10, IL-12, interferons (IFN)-alpha, IFN-gamma, tumor necrosis factor (TNF)-alpha, transforming growth factor-beta, and chemokines (CCL2, CCL3, CCL5, CXCL8, y/o CXCL10). This begins the so-called "cytokine storm", which is critical for the multi-organ failure leading to high lethality observed in affected patients[12,19-22].

The neuroinflammation caused by SARS-CoV-2, secondary to the cytokine storm and immune cells reactivation, also becomes an additional effect of CoV infection[21]. In this context, several pathways have been discussed regarding the strong immune response in humans secondary to SARS-CoV-2 infection[22]. A marked reduction in absolute count of T cells, monocytes, eosinophils, and basophils has been found during this infection, with a main impact on the absolute decrease of T cells, memory T helper and regulatory cells[23,24].

Besides the explosive cytokine release syndrome and the macrophage activation syndrome co-existing in SARS-CoV-2 infection and affecting the CNS, there is also a strong increase in pro-inflammatory cytokines, such as IL-6, IL-2, IL-17, granulocyte-colony stimulating factor and TNF[24]. Inflammatory conditions can also induce the increase of IL-1, IL-6 and TNF soluble mediators that might facilitate major BBB permeability[25], as they have been responsible for neurological manifestations such as encephalitis, CNS demyelination and neuropsychiatric disorders[26].

Even in the absence of SARS-CoV-2 CNS infiltration, a transmigration of peripheral cytokines derived from the systemic host antiviral response may also take place to induce neuropsychiatric symptoms by the neuro-inflammatory response and BBB disruption. This may be caused by the peripheral effector immune cells migrating into the CNS, as well as local impairment of the neurotransmission system[27,28]. High levels of neurotransmitters, mainly noradrenaline, epinephrine, and serotonin, have been associated with psychological manifestations, such as depression, anxiety, and post-traumatic stress disorder[20].

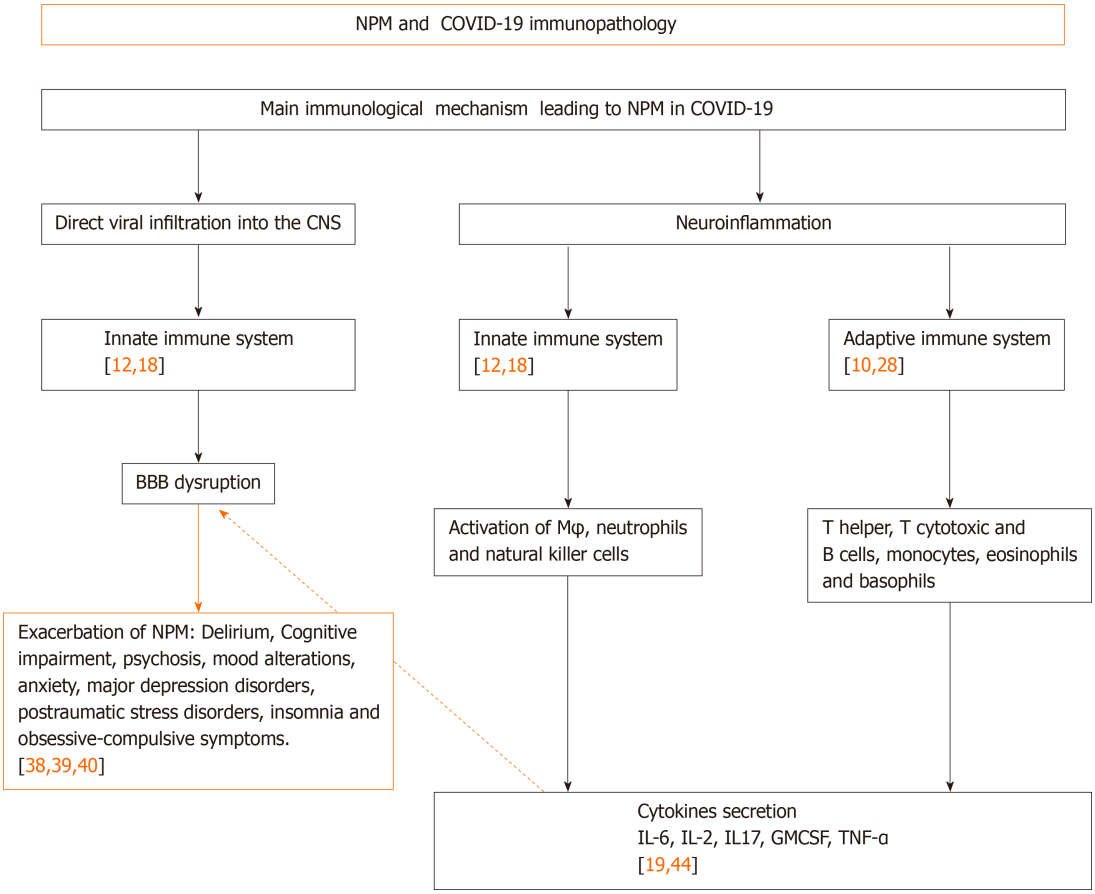


Figure 1 Immunological mechanisms of neuropsychiatric manifestations derived from severe acute respiratory syndrome coronavirus 2 infection. COVID-19: Coronavirus disease 2019; CNS: Central nervous system; NPM: Neuropsychiatric manifestation; M: Macrophages; BBB: Blood-brain barrier; GMCSF: Granulocyte-colony stimulating factor; IL: Interleukin; TNF: Tumor necrosis factor.

It seems possible that the hypothesis of cytokine storm being associated with psychiatric manifestation induction is an indirect consequence of the hyperinflammation. Previous studies regarding pandemics caused by respiratory viruses suggest that diverse occurrence of neuropsychiatric symptoms can take place during or after the acute infection, which may be underlined by the presence of persistent cognitive deficits.

In the COVID-19 acute phase, besides the psychosocial stressor factors, it has been argued that the infection underlying the pathophysiology of neuropsychiatric manifestations, such as encephalopathy, psychosis, insomnia, and mood changes, post-traumatic stress disorder, panic attacks, and anxiety, mostly seen in health care workers and survivors of SARS-CoV infection, have been mainly attributed to viral infection *per se* and secondary to the host immune response. In this way, direct viral infiltration of the CNS can trigger an inflammatory reaction at the brain level leading to local microglial activation, which in turn induces demyelinating processes that are one of the primary causes of encephalopathy. In the absence of direct viral infiltration, a peripheral cytokine storm causing an imbalance of neurotransmitters within the CNS has been implicated in neuropsychiatric manifestations. This cytokine storm induces a neuroinflammatory response causing disruption of the BBB, leading to peripheral immune cell transmigration into the brain and, in turn, causes imbalances in neurotran -smission.

It continues to be a challenge for researchers to elucidate the real core mechanisms of COVID-19 associated neuropsychiatric complications due to general findings caused by SARS-CoV-2 infection. This may be difficult to distinguish from the encephalopathy arising from systemic infection without affecting brain tissue[29]. Evidence such as the increase in IL-6 has been linked to high mortality in patients with COVID-19[19], similar to the increase in this cytokine observed in other neuropsychiatric disorders such as schizophrenia and depression[19].

Other arguments underlining the immunological mechanism identify that peripheral myeloid cells are also infected by CoV[5], which can be recruited to

transmigrate to the CNS under an increased BBB permeability. Virus-infected monocytes in the CNS can promote microglial activation as well as induce neuropsychiatric symptoms[5,27,28]. The role of microglial activation in schizophrenia and autism is well known[30,31,32]. Other mechanisms implicating mental disease in COVID-19 are the close inter-relation between the systemic compartment and the brain[7] (Figure 1).

NEUROPSYCHIATRIC FINDINGS IN THE COVID-19 PANDEMIC

Since the initial phase of the COVID-19 pandemic, a large number of studies have shown the clinical symptoms and signs of the infection. These principally include fever, cough, sore throat, dyspnea, nausea, diarrhea, and fatigue[27,33]. However, numerous reports also reveal an accumulation of frequent neurological symptoms in COVID-19 positive patients, such as dizziness, ageusia, fatigue, headache, impaired consciousness, and anosmia[34-36].

Parallel to the neurological events, evidence is growing for neuropsychiatric disorders that are also reported as secondary complications of SARS-CoV-2 infection [37], which will be made clear in the few years. In this context, an exacerbation of mental health disorders has been described in COVID-19 that include delirium, cognitive impairment, mood alterations, and psychosis[38-40]. Delirium occurs in 90% of COVID-19 cases, while cognitive disorder is also considered a direct consequence of CNS infection by SARS-CoV-2[39]. Anxiety, depression, post-traumatic stress disorder, insomnia, and obsessive-compulsive symptomatology, mainly in females, appear to be quite common in COVID-19 survivors and coworkers with worsened scores on psychopathological measures in those with a history of psychiatric comorbidities. In addition, hypoxemia, a frequent clinical finding in COVID-19, can also produce mental health impairment[38]. Thus, a consequence of acute respiratory syndrome and associated relative hypoxia also shows worsening of attention, executive function, and verbal memory[41].

An exaggerated immune response, under a dysregulated cytokine network, occurring during the COVID-19 pandemic would also drive symptoms of visceral stress with an impact on mental health[38,42]. In this line of thinking, authors have defined a relationship between COVID-19 disease severity, somatic and psychiatric symptoms, and cytokine levels in patients positive for SARS-CoV-2 infection. There is also some evidence that patients with comorbidities and immunosuppression are more susceptible to developing psychiatric disorders, such as cognitive impairment, anxiety, and depression[43,44].

Considering the trajectory of the occurrence of COVID-19 around the world, from its beginnings in China in December 2019, it is clear that not only patients but also their family and the normal population are victims of the psychosocial impacts derived from this pandemic[42,45]. From this viewpoint, it is clearly necessary to investigate the behavioral aspects of this disease, either in the short- or long-term, to identify a more valuable strategy to control the transmission by carriers and assess the impact of COVID-19, not only in affected patients, but also in the general population. We are proposing a diagram regarding the impact of the immunological mechanism involved in SARS-CoV-2 infection by the occurrence of neuropsychiatric manifestation as a tool of acknowledgment of the way the disease progresses which could allow better management of the disease and prevention of the consequences in the short- or long-term.

The long-term neuropsychiatric consequences of SARS-CoV-2 infection have been demonstrated in a fraction of cases; however, they appear to be significant for the future due to the global burden of COVID-19. In this context, to understand the evolution and specificity of neuropsychiatric outcomes stemming from SARS-CoV-2 infection and to elucidate the pathogenic mechanisms involved in these events should be useful in targeting critical interventions for the prevention of mental disorders derived from COVID-19. Nevertheless, the work of psychologists and psychiatrists concentrated on handling the psyche at clinics and paraclinics looking for more effective evidence of recovery from the potential neurological consequences will not be enough. It will be necessary to develop programs and strategies to achieve a more humanist medical approach to promote the resilience of the individuals affected as well as their parents to avoid the long-term occurrence of mental disorders due to the lost connection between the body and the soul. This is the neurobiological substrate in the development of neuropsychiatric disorders as a consequence of COVID-19. Finally, an earlier understanding of the characteristics of neuropsychiatric outcomes stemming

from SARS-CoV-2 infection and their pathogenic mechanisms will be necessary as an intervention target to avoid the sub-acute or chronic neuropsychiatric consequences of SARS-CoV-2 infection.

CONCLUSION

According to the numerous articles published since the beginning of the COVID-19 pandemic, it could be surmised that the accumulated knowledge would be enough to understand many of the events occurring in this illness. However, there is not enough data to understand the long-term consequences of this disease. The neuropsychiatric dysfunctions as part of the group of disorders unknown in the evolutionary context of COVID-19 could also be the result of an exaggerated host response against SARS-CoV-2 infection. The impact on the permeability of the BBB which facilitates the migration of immune cells to the CNS and their deleterious effect on neural function, followed by deregulation of the cytokine network that affects mental health, are manifested more frequently by anxiety, cognitive impairment and major depressive disorder. More studies will continue to be necessary to address this topic.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 355-364

DOI: 10.5498/wjp.v11.i7.355

ISSN 2220-3206 (online)

MINIREVIEWS

History of the dopamine hypothesis of antipsychotic action

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Author contributions: Seeman MV is the sole author and has approved the final version.

Conflict-of-interest statement: I am the widow of one of the investigators mentioned in the text.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Canada

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0

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Abstract

The dopamine hypothesis of how antipsychotic drugs exert their beneficial effect in psychotic illness has an interesting history that dates back to 1950. This hypothesis is not to be confused with the dopamine hypothesis of schizophrenia; the aim of the latter is to explain the etiology of schizophrenia. The present review does not deal with schizophrenia but, rather, with the historical development of our current understanding of the dopamine-associated actions of the drugs that reduce the symptoms of psychosis. This historical review begins with the serendipitous discovery of chlorpromazine, a drug synthesized around a chemical core that initially served to produce man-made dyes. This molecular core subsequently contributed to the chemistry of antihistamines. It was with the aim of producing a superior antihistamine that chlorpromazine was synthesized; instead, it revolutionized the treatment of psychosis. The first hypothesis of how this drug worked was that it induced hypothermia, a cooling of the body that led to a tranquilization of the mind. The new, at the time, discoveries of the presence of chemical transmitters in the brain soon steered investigations away from a temperature-related hypothesis toward questioning how this drug, and other drugs with similar properties and effects, modulated endogenous neurotransmission. As a result, over the years, researchers from around the world have begun to progressively learn what antipsychotic drugs do in the brain.

Key Words: Chlorpromazine; Haloperidol; G-Protein coupled receptors; Binding assays; Receptor imaging; High affinity states

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Core Tip: This history starts with the synthesis of chlorpromazine in 1950 and traces the steps taken to discover how this drug, and related drugs, work to reduce, sometimes to reverse, the delusions and hallucinations associated with psychosis. The task to understand how these drugs work in the brain continues, as many unknowns remain.

Grade E (Poor): 0

Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: April 20, 2021
Revised: April 22, 2021
Accepted: June 22, 2021
Article in press: June 22, 2021
Published online: July 19, 2021

P-Reviewer: Soriano-Ursúa MA
S-Editor: Fan JR
L-Editor: A
P-Editor: Wang LYT



Citation: Seeman MV. History of the dopamine hypothesis of antipsychotic action. *World J Psychiatr* 2021; 11(7): 355-364
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/355.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.355

INTRODUCTION

The synthesis of chlorpromazine in 1950 marks the beginning of modern psychopharmacology. While the clinical usefulness of this drug was almost immediately recognized, it took another 20 years to begin to uncover its mode of action. This review covers the history of these years and the steps that were taken to arrive at the dopamine hypothesis of antipsychotic drug action. It more briefly also outlines how this hypothesis has fared over the ensuing years (Table 1).

HISTORY

Prior to the availability of chlorpromazine, many drugs had been used in psychiatry to tranquilize agitated patients, but this was the first psychoactive agent to not only calm patients, but also to decrease the intensity of their psychotic symptoms. Synthesized by Paul Charpentier of the French pharmaceutical company Rhône-Poulenc, chlorpromazine was the product of a long process that began in the mid-1800s, starting out as a search for a method to synthesize dyes. This search led, in 1883, to the identification by August Bernthsen of a molecular structure, which he called a phenothiazine nucleus, around which later generations of chemists began to make antihistamine drugs for the treatment of allergies. In 1947, the pharmaceutical company, Rhône-Poulenc, produced promethazine, a first generation antihistamine[1] (Figure 1).

Promethazine induced hypothermia in laboratory animals so, in 1949, French military surgeon, Laborit[2] tried giving it to soldiers in order to lower their body temperature and prevent shock before, during, and after surgical operations. He noted that promethazine induced a "euphoric quietude" in his soldiers[2].

Hoping to increase the potency of promethazine, on December 11, 1950, Charpentier *et al*[3] introduced a chlorine atom into one of the rings of promethazine (Figure 2).

The new drug was called RP (for Rhône-Poulenc) 4560. It was tested on rats and produced "detachment, slow reaction to stimuli, and a decrease in initiative." The compound was again sent for human trials to Laborit, now at the Val de-Grâce Hospital in Paris, and, because of its psychological effects in animals, to a variety of French psychiatrists as well.

The first published report of its effect in humans was by Laborit and his team in February 1952. They reported that the drug calmed anxious patients without producing oversedation[4]. Three psychiatrists reported on the effect of the drug one month later[5]. This team concluded that 50-100 mg of RP4560, diluted in a glucose solution and given intravenously to patients with mania, kept them calm for 3 to 18 h, as long as an analgesic or a barbiturate was administered concurrently.

In May 1952, psychiatrists Delay and Deniker[6] published their observation on the soothing effect of the drug in patients with psychosis[6]. In June, this team once again reported positive results[7]. Going on the theory that the drug worked by cooling the body, a therapeutic intervention commonly used by psychiatrists at the time[8-10], in July, Delay *et al*[11] published more detailed results of 8 cases treated with RP4560 [11]. They diagnosed six of these patients as suffering from acute mania, one was said to show "excited delirium." One patient showed "recurrent excitement" and was described as having "trouble thinking" and using "over rationalization." In today's classification systems, this patient might be diagnosed with schizophrenia. In this clinical group's hands, RP4560 was administered without adjuncts, by injection, with oral tablets substituted for injections usually by the 10th treatment day. The results were remarkable–calm was induced in all patients, with minimum sedation. This created such a sensation in psychiatric circles that, by November 1952, the drug had become available by prescription in France[12].

The pharmaceutical firm Smith Klein and French bought the American rights to the drug and, in 1954, received Food and Drug Administration approval to market it in the United States under the name, Thorazine. The advertisement in the May 1954 issue of the American Journal of Psychiatry read: "Thorazine is useful in controlling anxiety,

Table 1 Major steps in the dopamine hypothesis of antipsychotic drug action

Year	Major Advances
1950	Synthesis of chlorpromazine[3]
1952	Preliminary evidence of antipsychotic effect of chlorpromazine[6,7,11]
1958	Synthesis of haloperidol[16]
1960	Parkinson basal ganglia are deficient in dopamine[19]
1963	Neuroleptics raise level of monoamine metabolites[18]
1966	Neuroleptics may antagonize dopamine receptors[26]
1971	2 nmol haloperidol in plasma effective in psychosis[34]
1974	Synthesis of (+-) butaclamol[36]
1975	Tritiated haloperidol binds DA receptors[38]
1975	Effective neuroleptic dose correlates with D2 block[39]
1979	Multiple dopamine receptors[54]
1984	Bimodal D2 distribution in schizophrenia[45]
1984	High and low affinity states for D2[58]
1988	Cloning of the D2 receptor[63]
1988	*In vivo* imaging of D2 occupancy[47]
1990	Cloning of D3[67]
1999	Fast-off theory[71]
2000	Multiple genetic variants of D2 receptor[73-75]
2000	Impact of the D3 receptor[81]
2005	Impact of other neurotransmitter receptors[83]
2010	Impact of receptor heterodimers[85]
2017	Impact of D2 high affinity state[77]
2021	Structure and specificities of D1, D2 signaling complexes[79]

tension, agitation, confusion, delirium, or hostility, whether occurring in schizophrenic, manic-depressive, toxic, or functional states." [1]. In France and also in Canada[13-15], the drug was called Largactil. Since it was mainly used in hospitalized patients who, for the most part, suffered from psychotic disorders, it swiftly gained a worldwide reputation for being able to reverse the symptoms of psychosis.

The phenothiazine core molecule was malleable and comparably easy to copy so that compounds with very similar efficacy were readily produced. By 1964, a variety of pharmaceutical companies had synthesized and marketed their own phenothiazines: promazine, trifluprom azine, methoxypromazine, trifluoperazine, fluphenazine, thioridazine, and prochlorperazine. In 1958, haloperidol, a non-phenothiazine drug [a butyrophenone synthesized on the base of an opioid analgesic, meperidine (Demerol)] was created by pharmaceutical genius, Paul Janssen. This compound proved to be more potent against delusions and hallucinations than the phenothiazines[16].

Both phenothiazines and butyrophenones were initially called 'major tranquilizers' to distinguish them from the 'minor tranquilizer,' meprobamate[17], which was being widely marketed at the time for anxiety.

Searching for the mode of action of major tranquilizers, in 1963, Carlsson and Londqvist[18] reported that this category of drugs increased the level of metabolites of catecholamines. They suggested ''. . . that chlorpromazine and haloperidol block monoaminergic receptors in brain . . . .'' It was not possible at the time to selectively distinguish among alpha-adrenoceptors, beta-adrenoceptors, and dopamine receptors.

There were, nevertheless, several reasons to believe that it was the dopamine pathway that was involved. Firstly, the clinical side effects of chlorpromazine and haloperidol were tremor, rigidity, and akinesia -*e.g.* Parkinsonian signs and, by then, Parkinson's disease had been linked to a deficiency of dopamine[19]. Secondly, it had already been suggested that dopamine-mimetic drugs such as amphetamine acted *via*

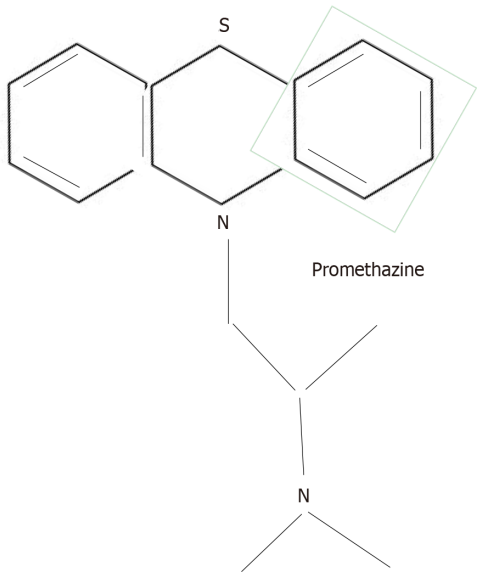


Figure 1 Promethazine.

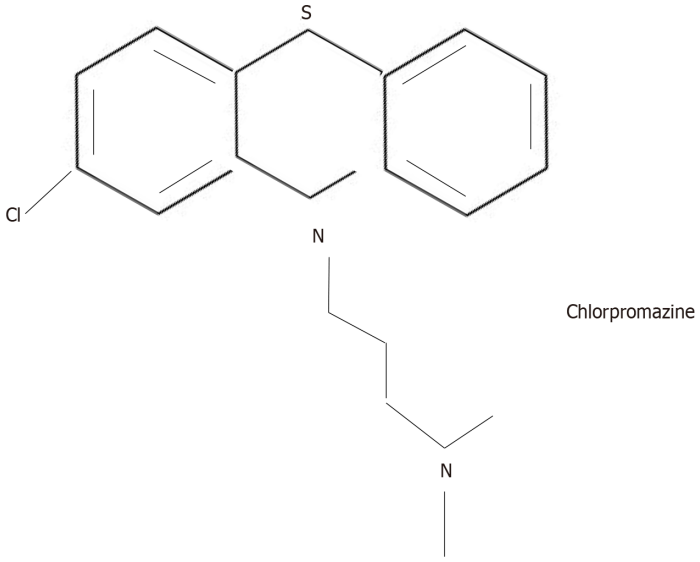


Figure 2 Chlorpromazine.

dopamine receptors[20] and that amphetamines could induce schizophrenia-like psychotic symptoms in patients[21,22]. Disulfiram (Antabuse), in clinical use to prevent alcohol addiction, was known to inhibits dopamine beta-hydroxylase, the enzyme that converts dopamine to noradrenaline, and this drug, too, was capable of inducing psychosis[23].

There were also reports of chlorpromazine accelerating the turnover of dopamine [24]. Van Rossum[25] had noticed in 1965 that major tranquilizers (or neuroleptics as they were called by this time), though not, as was first thought, particularly antiadrenergic, were, instead, potent amphetamine antagonists[25].

The significance of dopamine for the action of antipsychotic drugs, a breakthrough often attributed to Arvid Carlsson (who did not seriously consider dopamine in the context of the action of these drugs until much later) was first formulated by Jacques van Rossum. In 1966, van Rossum[26] hypothesized that dopamine receptor blockade was a likely explanation for the mechanism of action of this group of drugs. He referred to neuroleptics as the first available dopamine antagonists. In 1967, van Rossum[27] wrote: "When the hypothesis of dopamine blockade by neuroleptic agents can be further substantiated, it may have far going consequences for the pathophysiology of schizophrenia. Overstimulation of dopamine receptors could then

be part of the aetiology. Obviously such an overstimulation might be caused by overproduction of dopamine, production of substances with dopamine actions (methoxy derivatives), abnormal susceptibility of the receptors, *etc.*"[27].

Van Rossum, thus, formulated *two* dopamine hypotheses (1) The hypothesis that dopamine receptor blockade was responsible for the antipsychotic effects of drugs like chlorpromazine, haloperidol, and similar drugs; and (2) The hypothesis that an excess of dopamine might be part of the etiology of schizophrenia. These two distinct hypotheses are often conflated[28].

They are conflated because, in the 1970s, it was hoped that the discovery of how neuroleptics work could lead to understanding the nature of schizophrenia itself. Based on the fact that amphetamine releases dopamine and amphetamine-induced psychosis is clinically very similar to an acute episode of schizophrenia[29], van Rossum[27] thought that schizophrenia might be due to an overproduction of dopamine[27].

From today's standpoint, overactivity of dopamine, while possibly explaining the hallucinations and delusions of schizophrenia, does not shed light on the more fundamental negative and cognitive symptoms of schizophrenia. Over the years, many attempts have been made to elaborate and expand on van Rossum's dopamine hypothesis of schizophrenia to account for symptoms other than delusions and hallucinations[30,31]. It remains the case, however, that schizophrenia is too multifaceted and heterogeneous a disorder to be fully explained by dopamine overactivity alone. That being said, it is still possible that the secretion and transmission of dopamine serves as a final common pathway to the expression of specific schizophrenia symptoms[32].

Van Rossum's first hypothesis-that neuroleptics (today referred to as antipsychotics) exert their effect through dopamine receptors–has enjoyed a longer life than his second. In 2020, Kaar *et al*[33], in their review of mechanisms underlying clinical response to antipsychotics, conclude that "all currently licensed antipsychotic drugs show appreciable binding to dopamine D2 receptors at therapeutic doses, and this action is core to their therapeutic action."

Van Rossum[25-27] had pointed out that overstimulation by dopamine could result from a number of potential causes, from overproduction by the secreting cell to oversensitivity of receptors on the post-synaptic cell. By extension, antipsychotic drugs could theoretically act by blocking dopamine synthesis or secretion or by interfering with its transport across the synapse or by blocking membrane receptors.

In 1971, Zingales[34] reported that the concentration of haloperidol in the plasma of treated patients was approximately 3 nanograms *per* millilitre of plasma (3 nmol)[34]. Because over 90% of haloperidol in plasma is bound to plasma proteins, the actual free concentration that enters the brain would then have to be approximately 1 nmol. This was a problem for the radioactive tagging needed in the search for specific targets of haloperidol action. The classical way to find a drug target was to tag the drug with a radioactive marker. In this case, however, because the drug needed to be diluted down to 1 nmol and still have enough radioactivity left for the experiment to succeed, the radioactive label had to be extra powerful. No such label existed at the time.

In November 1971, Philip Seeman, a Toronto physician/pharmacologist, asked Paul Janssen to persuade the company, I.R.E. Belgique, to prepare radioactive haloperidol at a high specificity of 10.5 Curies *per* millimole, which the company succeeded in doing in 1974.

True drug receptor targets have to take up the radioactively labelled ligand; a second important criterion in identifying a specific site of action is stereoselectivity–the configuration of the relevant molecule must fit the configuration of the target[35]. Seeman obtained mirror image antipsychotic molecules (+butaclamol and -butaclamol), the first one active, the second inactive[36,37]. A specific antipsychotic target was confirmed when the site was blocked by +butaclamol to a significantly greater degree than it was by -butaclamol. This more or less settled the identity of the antipsychotic receptor. A further step was to see which of the endogenous neurotransmitters had the most affinity for this location. When tested against noradrenaline, acetylcholine, serotonin, and dopamine, dopamine proved to be the most potent. This meant that the antipsychotic receptor was a dopamine receptor[38].

Soon after discovering the receptor, Seeman *et al*[39,40] showed that the published clinical doses of all antipsychotic drugs available at the time, regardless of their molecular structure, directly correlated with their ability to displace radioactive haloperidol[39,40]. This graph has recently been called "the most famous graph in schizophrenia therapeutics."[41]. The findings from the Seeman laboratory were soon confirmed by binding studies from other labs[42-44]. A further confirmatory finding was that treatment with antipsychotic drugs increased the density of dopamine

receptors in post mortem brain tissue of individuals with schizophrenia[45].

In vivo molecular imaging studies were not initially available but, when they were, they were eventually able to confirm striatal dopamine D2 receptor blockade at clinically effective doses of all antipsychotic drugs, including first and second-generation agents and dopamine partial agonists[46-52]. The initial molecular imaging studies in patients with treated schizophrenia suggested a therapeutic window (relatively good response without unacceptable extrapyramidal adverse effects) of between 60% and 80% D2 receptor occupancy. The definition of 'response,' of course, varies and non-response did not necessarily correlate with low occupancy rates[53].

Since then, the field of dopamine receptors has considerably expanded[54]. The receptor labeled by [3H] haloperidol was called D2[55,56], because, by the mid 1980s, five dopamine receptors, all belonging to a G-protein coupled set of receptors, had been isolated. Today, D1 and D5 are known to stimulate the cyclic adenosine monophosphate signaling pathway through G_s G-proteins, whereas D2R, D3, and D4 inhibit this signal *via* G_i/o G-proteins[57]. Moreover, each of these receptors can exist, as can all G-protein linked receptors, in a state of high or low affinity for their ligand [58,59]. Of the 5 known dopamine receptors, D1, D4, and D5 were cloned in the Seeman laboratory[60-62].

The dopamine D2 receptor was cloned in 1988 in the Civelli lab[63,64]. In 1989, Grandy *et al*[65] used in situ hybridization to map the gene to the 11q22–q23 junction.

Because of the excellent correlation between the affinity for striatal D2 receptors and the average clinical dose of antipsychotic drugs given to patients with schizophrenia, there was at first general agreement that all effective antipsychotic drugs must act by not only blocking dopamine D2 receptors in the striatum, but also blocking them in the mesolimbic system, where symptoms of psychosis are thought to originate[66].

In 1990, the D3 receptor (closely related to D2) was cloned in the laboratory of Jean-Claude Schwartz[67].

Soon after, the 2nd generation antipsychotic drugs were brought to market, and they appeared to have much lower affinity for the D2/D3 receptors (they induced far fewer extrapyramidal symptoms) but to be just as potent against psychotic symptoms (delusions and hallucinations) as the older drugs. Clozapine, in particular, the best antipsychotic in that patients resistant to all other drugs often respond when prescribed clozapine, attached to many neurotransmitter receptors besides D2/D3 [68]. Many of the new drugs[69], including clozapine[70] had affinity for serotonin 2AR, which was thought explain their much lower relative rate of extrapyramidal effects.

Another explanation was that the antipsychotics drugs that do not elicit extrapyramidal symptoms, such as clozapine and quetiapine, bind to the D2 receptor more loosely than dopamine itself so that endogenous dopamine displaces them very quickly from the target receptor. Drugs that bind most tightly to the D2 receptor (chlorpromazine, trifluoperazine, fluphenazine, haloperidol, risperidone) stay on the receptor for 20-30 min and it is this long continuous occupation that may be responsible for parkinsonism[71,72]. This explanation suggests that, though a certain threshold percentage of D2 receptors still need to be bound in order to obtain an antipsychotic effect, the binding need not be of long duration. 'Hit and run' or 'fast-off' binding is able to prevent some of the adverse effects while still maintaining efficacy against psychosis.

An unresolved continuing problem with respect to antipsychotic drug action is that at least one third of patients with schizophrenia do not respond to drugs that block D2, whether transiently or for long periods, whether with or without serotonin 2A binding. One possible explanation is that individuals inherit different genetic variants of the D2 receptor[73-76], and that these variants determine response. Since the functional state of the dopamine receptor in the anterior pituitary[58], and perhaps everywhere in the brain[77], is its high affinity form, it is perhaps the relative duration of time that these receptors spend in their various affinity states that determines the extent of clinical response. It has been hypothesized that an interaction between D1 and D2 receptors influences the time spent in the high affinity functional state[78]. Every year, more knowledge accumulates about the signaling complexes of D1 and D2 receptors[79] and new radioactive ligands are available that bind specifically to high affinity sites[80].

Although binding to the D2 receptor continues to be considered as the cornerstone of antipsychotic action, the original hypothesis has undergone several refinements, such as the acknowledgement that other dopamine receptors as well as other neurotransmitter receptors play a part[81-84]. There now exist effective antipsychotic drugs that defy the earlier established D2 receptor occupancy threshold, which makes it difficult to attribute antipsychotic effect to any single neurotransmitter receptor[85-

87].

CONCLUSION

Dopamine D2 receptor blockade remains necessary in order to obtain antipsychotic response in most patients. Individuals differ, however, and it remains possible, even probable, that specific subgroups of patients showing psychotic symptoms may respond most robustly to pharmaceutical agents that mainly affect brain chemical transmitters other than dopamine. Pimavanserin, for instance, a serotonin 2A receptor antagonist, has had some success in treating the psychosis associated with Parkinson's disease, a condition of dopamine deficiency[88], but the Food and Drug Administration in the United States has recently found it insufficiently effective for the psychosis associated with Alzheimer's dementia. Differently caused psychoses may respond to differently configured drugs. Looking for the mechanism of action of drugs for psychosis continues, and, as new mechanisms are found, the secrets of the multiple causes of psychotic disorders may be decoded.

ACKNOWLEDGEMENTS

Thank you to Dr. Gary Remington for suggestions and editing.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 365-374

DOI: 10.5498/wjp.v11.i7.365

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Clinical and Translational Research

Role of perceived family support in psychological distress for pregnant women during the COVID-19 pandemic

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Author contributions: Zhang XY and Zhou YJ designed the study, and jointly directed this work; Yuan ZJ, Leng WC, Xia LY and Wang RX were responsible for collecting the data; Zhou YJ and Wang YN collected literatures, cleaned data and did statistical analysis; Wang YN wrote the manuscript; Zhang XY and Li ZZ reviewed and revised the manuscript.

Supported by Lanzhou Science and Technology Project, No. 2020-XG-71.

Institutional review board statement: The protocol of the study was approved by the ethics committee of the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences.

Informed consent statement: All participants provided the informed consent before participating in the

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has caused major public panic in China. Pregnant women may be more vulnerable to stress, which may cause them to have psychological problems.

AIM

To explore the effects of perceived family support on psychological distress in pregnant women during the COVID-19 pandemic.

METHODS

A total of 2232 subjects were recruited from three cities in China. Through the online surveys, information on demographic data and health status during

pregnancy were collected. Insomnia severity index, generalized anxiety disorder 7-item scale, patient health questionnaire-9, somatization subscale of the symptom check list 90 scale, and posttraumatic stress disorder checklist were used to assess the psychological distress.

RESULTS

A total of 1015 (45.4%) women reported having at least one psychological distress. The women who reported having inadequate family support were more likely to suffer from multiple psychological distress (≥ 2 psychological distress) than women who received adequate family support. Among the women who reported less family support, 41.8% reported depression, 31.1% reported anxiety, 8.2% reported insomnia, 13.3% reported somatization and 8.9% reported posttraumatic stress disorder (PTSD), which were significantly higher than those who received strong family support. Perceived family support level was negatively correlated with depressive symptoms (r = -0.118, P < 0.001), anxiety symptoms (r = -0.111, P < 0.001), and PTSD symptoms (r = -0.155, P < 0.001).

CONCLUSION

Family support plays an important part on pregnant women's mental health during the COVID-19 pandemic. Better family support can help improve the mental health of pregnant women.

Key Words: Pregnant women; Perceived family support; Coronavirus; Psychological distress

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Core Tip: The coronavirus disease 2019 (COVID-19) pandemic has caused major public panic in China. Pregnant women may be more vulnerable to stress, which may cause them to have psychological problems. The purpose of this study was to explore the effects of perceived family support on psychological distress in pregnant women during the COVID-19 pandemic. We found that family support plays an important part on pregnant women's mental health during the COVID-19 pandemic. Better family support can help improve the mental health of pregnant women.

Citation: Wang YN, Yuan ZJ, Leng WC, Xia LY, Wang RX, Li ZZ, Zhou YJ, Zhang XY. Role of perceived family support in psychological distress for pregnant women during the COVID-19 pandemic. *World J Psychiatr* 2021; 11(7): 365-374
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/365.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.365

INTRODUCTION

The outbreak of the coronavirus disease 2019 (COVID-19) is a global health threat[1] and is listed by World Health Organization (WHO) as a Public Health Emergency of International Concern (PHEIC). According to WHO data, there were 72546247 confirmed cases and 1614014 deaths worldwide[2]. In China, there are more than 90000 confirmed cases, with deaths exceeding 4758[2]. Corona viruses mainly cause respiratory diseases, ranging from the common cold to severe respiratory diseases, with a fatality rate of around 1%[3].

The COVID-19 pandemic seriously threatens people's physical health and can trigger various psychological crises. COVID-19 was associated with increased psychological distress not only in the general population[4], but also in clinical samples[5]. Importantly, women are more vulnerable to psychological distress, when experiencing disasters or traumatic events, compared to men[6]. During the outbreak of COVID-19, approximate 35% of the 52730 people in China experienced psychological distress[7]. Another online survey showed that during the COVID-19 outbreak, among the general Chinese population, 31.3% of participants had depressive symptoms and 36.4% of participants experienced anxiety[8]. In both studies, women showed higher

study.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

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Manuscript source: Unsolicited manuscript

Specialty type: Psychiatry

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 10, 2021
Peer-review started: February 10, 2021
First decision: May 5, 2021
Revised: May 8, 2021
Accepted: June 17, 2021
Article in press: June 17, 2021
Published online: July 19, 2021

P-Reviewer: Janiri D
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Li JH

levels of stress, anxiety and depression[7,8]. The impact of the epidemic on women's mental health is significantly higher compared to men[7,8].

As the changes in the level and function of the endocrine system during pregnancy, pregnant women often experience great mood swings and even mental disorders, such as anxiety[9], depression[10]. During the COVID-19 pandemic, pregnant women may suffer extra psychological stress for worrying about the adverse effects on their offspring caused by 2019-nCoV. A recent study reported that after the announcement of the COVID-19 epidemic, the prevalence of depressive symptoms among pregnant women was spiked as to before the announcement[11].

In Wuhan city, a total of 50340 have been confirmed of COVID-19, making it the worst-hit area in China. Wuhan was cordoned off 3 wk after the outbreak. To prevent infection, most all of Wuhan residents had to stay at home and isolated from society. Loss of income was the following stress for them. As a result, most Wuhan residents may not only suffer from the epidemic, but also suffer from isolation, stress and the loss of income[12].

Women who have supportive networks of friends and family may experience less stress and have better mental health conditions. Conversely, poor family relationships and social support might be associated with depressive symptoms[13]. A longitudinal study in pregnancy has found that partnership tension was the only predictor of women's transient and chronic anxiety during pregnancy or postpartum period[14]. The active support of the partner is a critical factor affecting the mental health of pregnant and postpartum women, and the support of the extended family is also important for the mental health conditions of pregnant women[14].

For family-centered Chinese culture, family support is probably the most important sources of social support[15]. Chinese women pay more attention to the family and are more susceptible to family relationships, compared with western women[16]. However, in the context of COVID-19 pandemic, it is unknown whether good family support can still benefit the psychological status of women. Therefore, after the announcement of the coronavirus epidemic in China, we conducted a mental health survey for pregnant women in different provinces of China, including Wuhan (Confirmed COVID-19 case > 60000), Beijing (Confirmed COVID-19 case: 581) and Lanzhou (Confirmed COVID-19 case: 24) in China. In addition, economic loss caused by COVID-19, characteristics related to pregnancy was investigated. The hypothesis of the study is that perceived family support is more important for the mental health of women during pregnancy than the economic loss caused by COVID-19 and the severity of the COVID-19.

MATERIALS AND METHODS

Participants

A cross-sectional survey was performed in this study after the Chinese government announced the coronavirus epidemic (from February 1 to April 28, 2020). The women during pregnancy were invited electronically to complete an anonymous online questionnaire in Wuhan, Beijing and Lanzhou by social media app WeChat (WeChat, Tencent Inc, China), since the Chinese government demanded the public staying at home. The questionnaire was disseminated through notifications from the maternal and child health hospitals. As a result, a total of 2232 valid responses were received from Wuhan (34.8%), Beijing (40.2%) and Lanzhou (25.0%).

The protocol of the study was approved by the ethics committee of the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences. All participants provided the informed consent before participating in the study.

Questionnaire survey

A structured questionnaire was used to collect personal data, including socio-demographic variables, information of pregnancy, information of psychological distress, information about COVID-19 and the perceived family support in pregnancy. The socio-demographic variables included age, nationality, marital status, occupation, and education. The information of pregnancy included gestational age, parity, period and pregnancy complications. The information of psychological distress of the participants was assessed by the Chinese version of 5 international validity scales, include insomnia severity index (ISI), generalized anxiety disorder 7-item scale (GAD-7), patient health questionnaire-9 (PHQ-9), somatization subscale of the symptom check list 90 scale (SCL-90) and posttraumatic stress disorder checklist (PCL-5). Information about COVID-19 included income loss caused by COVID-19 and whether

or not their relatives or friends were infected with COVID-19.

ISI is a 7-item self-report questionnaire that assesses the severity and impact of insomnia[17]. Each item is rated on a 5-point scale (0 = no problem; 4 = very severe problem), with a total score ranging from 0 to 28. The total score is interpreted as follows: No insomnia (0-7); sub-threshold insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28)[18]. Participants with a total score ≥ 15 were rated as having insomnia in this study. GAD-7 is a tool for assessing the severity of generalized anxiety. The 7 items are rated on a 3-point Likert scale, with a total score ranging from 0 to 21 (0–4: Normal; 5–9: Mild anxiety; 10–14: Moderate anxiety and 15–21: Severe anxiety). Clinically significant anxiety can be detected when the total score reaches 5 or above[19,20]. PHQ-9 is a 9-item instrument for assessing the presence and severity of depressive symptoms. The PHQ-9 specially includes 9-item diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), on which the clinical diagnosis of depressive disorder is based[21]. Each item is rated on a 3-point scale (0 = no symptom; 3 = presence of symptom almost every day), with a total score ranging from 0 to 27(0–4: Normal; 5–9: Mild depression; 10–14: Moderate depression, 15–19: Moderately severe depression, and 20-27 severe depression)[21]. In this study, participants with a total score ≥ 5 were rated as suffering from depression. SCL-90[22] somatization subscale was used to assess the severity of somatization symptoms. The responses to these 12 items can be scored from 0 (none) to 4 (too much) on a Likert scale, with a total score ranging from 12 to 60. Participants with a total score ≥ 24 were rated as having somatic symptoms in this study. PCL-5[23] was used to assess the presence and severity of posttraumatic stress disorder (PTSD) symptoms. This is a 20-item self-report scale. Respondents were rated on a 5-point scale ranging from 0 (not at all) to 4 (extremely) to indicate how much troubled they have been in the past month according to PCL-5. The recommended PCL-5 cut-off score for the diagnosis of PTSD is 33[24]. In this study, participants with a total score ≥ 33 were rated as suffering from PTSD.

The perceived family support level was measured with the items of objective support from family numbers (husband, parents, parents-in-law, sisters / brothers, children and other family members) of Social Support Rating Scale (Chinese version) [25]. Participants rated on a 4-point scales (1 = none, 2 = rarely, 3 = some support/care, 4 = strong support/care)[15].

Statistical analysis

Analysis of variance was used to compare continuous variables, and χ^2 test were used for categorical variables. Spearman correlation analysis was performed to examine the relationship between perceived family support level and the five types of maternal psychological distress. Multiple linear regression was performed to examine the linear relationship between the scores of ISI, GAD-7, PHQ-9, SCL-90, PCL-5 and family support levels. In addition, a binary logistic regression analysis was conducted to estimate the association between perceived family support and psychological distresses by calculating odds ratio (OR) and 95% confidence interval (CI).

All analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, United States). All tests were two-tailed, and the statistical significance was defined at $P < 0.05$.

RESULTS

Sample characteristics

The socio-demographic characteristics of the participants are shown in Table 1. Women with a history of mental illness were not excluded from this study due to the small proportion (13 women).Significant differences were found between the women with and without psychological distress in terms of age ($\chi^2 = 2.16$, $P = 0.031$), region ($\chi^2 = 89.7$, $P < 0.001$), educational level ($\chi^2 = 13.61$, $P = 0.001$), annual household income ($\chi^2 = 10.23$, $P = 0.017$), income loss caused by COVID-19 ($\chi^2 = 13.83$, $P = 0.003$) and perceived family support ($\chi^2 = 13.57$, $P = 0.001$).

Psychological distress in different perceived family support levels

A total of 1015 (45.4%) women reported at least one instance of psychological distress. As shown in Figure 1, more women with less or some family support reported suffering multiple instances of psychological distress (≥ 2 type of psychological distress) than those with strong family support. A total of 5.2% of women with less family support reported having four types of psychological distress and 5.9% of them

Table 1 Demographic characteristics of responded women

Characteristics	*n* (%)	Psychological distress	No psychological distress	F/χ^2	*P* value
Age (mean ± SD, yr)	30.25 ± 3.99	30.05 ± 3.99	30.42 ± 3.98	2.16	0.031
Region, *n* (%)[1]				89.71	< 0.001
Wuhan	777 (34.8)	382 (49.2)	395 (50.8)		
Peking	897 (40.2)	306 (34.1)	591 (65.9)		
Lanzhou	558 (25.0)	327 (58.6)	231 (41.4)		
Marital status, *n* (%)				3.70	0.069
married	2179 (97.6)	984 (45.2)	1195 (54.8)		
Single, separated, divorced or widowed	53 (2.4)	31 (58.5)	22 (41.5)		
Educational level, *n* (%)				13.67	0.001
< 14 yr	1016 (45.6)	504 (49.6)	512 (50.4)		
≥ 14 yr	1216 (43.7)	511 (42.1)	705 (57.9)		
Annual household income (CNY), *n* (%)				10.23	0.017
< 80000	706 (31.6)	350 (49.6)	356 (50.4)		
80000	1255 (56.2)	552 (43.9)	703 (56.1)		
≥ 300000	273 (12.2)	113 (41.4)	160 (58.6)		
Income loss caused by COVID-19(CNY), *n* (%)				13.83	0.003
< 20000	862 (38.7)	331 (38.8)	522 (61.2)		
≥ 20000	1362 (61.3)	673 (50.7)	692 (49.3)		
Employment status, *n* (%)				0.01	0.999
Employed	1496 (67.1)	681 (45.5)	815 (54.5)		
Housewife	736 (32.9)	334 (45.4)	402 (54.6)		
Perceived family support level, *n* (%)				13.57	0.001
Less[2]	134 (6.0)	71 (53.0)	63 (47.0)		
Some	466 (20.9)	246 (52.8)	220 (47.2)		
Strong	1632 (73.1)	706 (43.3)	926 (56.7)		

[1]Confirmed COVID-19 cases in participating city: Wuhan: > 50000 cases; Beijing: 581 cases; Lanzhou: 24 cases.
[2]Participants rated on "none" and "rarely" scale.

had five types of psychological distress, which was significantly higher than those with some family support (3.2%,1.3%) or those with strong family support (2.6%, 0.7%).

Women with less or some family support reported significantly higher rates of psychological distress than women with strong family support (all $P < 0.05$). Among women with less family support, 41.8% reported depression, 31.1% reported anxiety, 8.2% reported insomnia, 13.3% reported somatization and 8.9% reported PTSD (Table 2).

Association between family support and psychological distress

The perceived family support levels negatively correlated with depressive symptoms (PHQ-9 score, $r = -0.118$, $P < 0.001$), anxiety symptoms (GAD-7 scores, $r = -0.111$, $P < 0.001$), and PTSD symptoms (PCL-5 score $r = -0.155$, $P < 0.001$). Logistic regression results showed there was a significant association between perceived family support and psychological distress of pregnant women (Table 3). After adjusting for age, marital status, region, educational level, annual household income, and income loss caused by COVID-19, less perceived family support displayed a significant association with anxiety (GAD-7 score ≥ 5, OR = 1.98, 95%CI: 1.32-2.96, $P < 0.01$), insomnia (ISI score ≥ 15, OR = 3.47, 95%CI: 1.68-7.16, $P < 0.01$), and PTSD (PCL-5 score ≥ 33, OR = 6.69, 95%CI: 3.07-14.55, $P < 0.01$) (Table 3).

DISCUSSION

To our best knowledge, this is the first study to explore the relationship between perceived family support and psychological distress in pregnant women during major life-threatening public health events. In this study, we had 3 main findings: (1) A significant proportion (45.4%) of pregnant women reported at least one psychological distress during COVID-19 pandemic; (2) The risk of insomnia, anxiety and PTSD in women with less family support was 3.46 times, 1.97 times and 6.69 times higher than that in women with strong perceived family support, respectively; and (3) Depression symptoms (PHQ-9 score), anxiety symptoms (GAD-7 score) and PTSD symptoms (PCL-5 score) were significantly negatively associated with perceived family support.

It is speculated that residents living in Wuhan suffered from higher levels of psychological distress, because this place was most affected by the epidemic[7] in mainland China. This may also increase the risk of psychological distress in pregnant women[11]. Interestingly, our study did not find an increase in the rate of maternal psychological distress amongst women in Wuhan. On the contrary, more women living in Lanzhou reported suffering from psychological distress, though it was only 24 confirmed COVID-19 cases in Lanzhou. That may be due to the fact that more women living in Lanzhou reported insufficient support from family numbers than women living in Beijing and Wuhan. The results showed that depression (35.6%) and anxiety (22.0%) were the most common disorders reported by pregnant women. In addition, at the peak of the COVID-19 epidemic, the pregnant women also suffered from somatization (8.1%), insomnia (3.4%) and PTSD (2.3%). The findings were similar to those of previous studies, indicating that pregnant women may be more vulnerable to depression in the context of the COVID-19 epidemic. A recent study reported that during the COVID-19 epidemic, the depression rate amongst Chinese pregnant women rose to 29.6%[11]. Another study showed that 28.8% of Danish women had anxiety/depressive symptoms during the COVID-19 pandemic[26].

There is extensive evidence that psychological distress during pregnancy are thought to increase the risk of developing psychological dysfunction in the offspring [27]. Pregnancy are very special periods for women. Affected by changes in the level and function of the endocrine system during pregnancy, mothers often experience huge mood swings and even mental disorders, such as anxiety[9], depression[10], and sleep disturbance[28]. The prevalence of depression in pregnant and postpartum women was estimated to be between 7% and 25%[10,26,27], and the prevalence of anxiety disorders is estimated to be between 4% and 39%[29]. However, our results showed that with different levels of family support, there were significant differences in the proportion of women with mental disorders during pregnancy. Women with inadequate family support were more likely to suffer from multiple psychological distresses. The strengthening of family support, the reporting rate of maternal psychological distress reduced. These findings highlight the essential role of adequate family support in mental health of pregnant women through major life-threatening public health events.

Social support, including supports from family members, colleagues, friends, neighbors, professionals, and organizations, is important for maternal mental health [15]. Due to the sudden outbreak, features and clinic symptoms of the COVID-19 are still unclear during the peak of the epidemic. The Chinese government intensified its management of the pandemic through public health interventions, such as strengthening some blockades, demand of staying at home. Hospitals had to terminate health care services for pregnant women to prevent infection, and most of them were trapped at home and isolated themselves from society. The confinement conditions have made the support of family members the only source of social support. In the general population, social support is widely regarded as a key factor in relieving perinatal depression[30]. A large number of studies have confirmed that family support has a positive effect on the level of perceived psychological stress[6,31-33]. According to Cohen[34], the relationship between perceived family support and life satisfaction was very strong.

Perceived family support makes a person feel cared for, loved, and dependent on family numbers when needed[33]. The levels of perceived family support can affect the way people deal with and adapt to stressful events, thereby reducing the negative effects on mental and physical health[6]. Therefore, adequate family support can alleviate the pressure caused by the COVID-19 outbreak. However, although physical care for pregnant women has been greatly improved in China in the past few decades, little attention has been paid to emotional care[15]. The findings of this study emphasized the importance of emotional care for pregnant women. The role and mechanism of family support in alleviating the negative psychological effects of

Table 2 Self-reported psychological distresses of pregnant women with different perceived family support level, *n* (%)

	Total	Less PFS	Some PFS	Strong PFS	F/χ^2	*P* value
Depression	795 (35.6)	56 (41.8)	207 (44.4)	532 (32.6)	24.15	< 0.001
Anxiety	491 (22.0)	42 (31.1)	128 (27.5)	321 (19.6)	19.79	< 0.001
Insomnia	77 (3.4)	11 (8.2)	15 (3.2)	51 (3.1)	9.72	0.008
Somatization	180 (8.1)	18 (13.3)	41(8.8)	121(7.4)	6.34	0.042
PTSD	52 (2.3)	12 (8.9)	14 (3.0)	26 (1.6)	30.41	< 0.001

PFS: Progress-free survival; PTSD: Posttraumatic stress disorder.

Table 3 Association between perceived family support [*n* (%)] and self-reported maternal psychological distresses

	Depression	Anxiety	Insomnia	Somatization	PTSD
Spearman correlation coefficient, *r*					
	-0.118[b]	-0.111[b]	-0.025	-0.038	-0.155[b]
Multiple linear regression, β					
	-0.973[b]	-0.638[b]	-0.195	-0.418	-2.238[b]
Logistic regression analysis, OR (95%CI)					
Strong support	1	1	1	1	1
Some support	1.56 (1.26-1.94)[b]	1.69 (1.24-2.04)[b]	1.13 (0.62-2.04)	1.02 (0.65-1.45)	1.91 (0.96-3.79)
Less support	1.33 (0.90-1.92)	1.98 (1.32-2.96)[b]	3.47 (1.68-7.16)[b]	1.41 (0.80-2.48)	6.69 (3.07-14.55)[b]

OR and 95%CI were estimated using binary logistic regression and adjusted for age, marital status, region place of residence, educational level, annual household income, income loss caused by COVID-19.
[b]$P < 0.01$.
PTSD: Posttraumatic stress disorder.

adverse events have not been clearly or fully explained. Further research is needed to understand the role and mechanism of this factor in order to utilize family support to help pregnant women in major life-threatening public health events.

However, several limitations have to be considered when interpreting these findings. Firstly, the data obtained from online surveys and maternal psychological distress relied on self-reported measurements. Women may inaccurately report the presence or absence of psychological distress. Secondly, although internationally valid and reliable questionnaires were utilized in this study, these questionnaires did not provide a diagnosis of mental disorders. Thirdly, the evaluation of family support used the subjective feelings of women rather than the social support rating scale. This may make our results less precise. Fourthly, other influencing factors such as family relationship, family conflict, and family resources are also important variables that affect the psychological well-being of pregnant and postpartum women, which were not taken into account in this study. Finally, a cross-sectional analysis of this study suggests that there is an association between maternal psychological distress and family support, rather than a causal relationship. Future research may focus on a longitudinal study to confirm causality.

CONCLUSION

The results of this study indicate that the COVID-19 pandemic has a negative impact on the mental health of Chinese pregnant women. Family support was significantly negatively correlated with psychological distress. Compared with women with strong family support, women with insufficient family support were more associated with the risk of anxiety, insomnia, depression and PTSD. This study shows that in major life-threatening public health events, family support has a positive impact on the

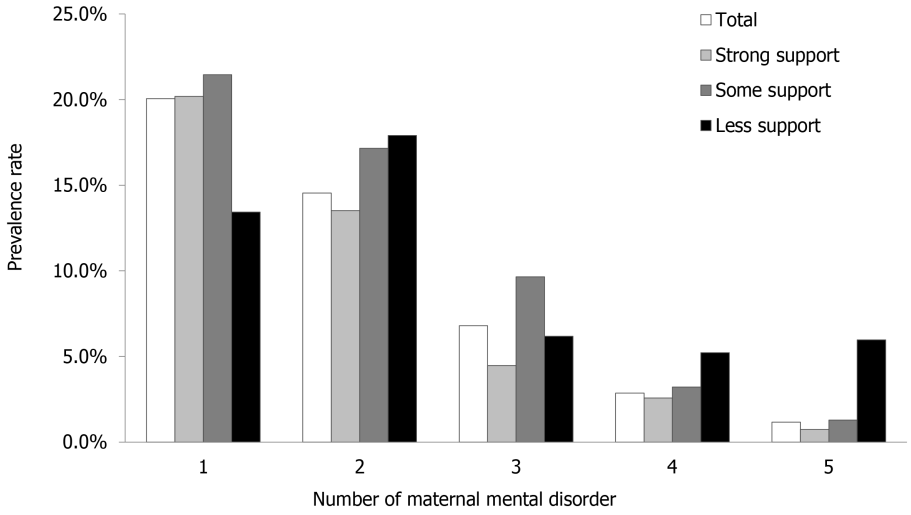


Figure 1 Frequency for self-reported multiple psychological distresses in different perceived family support level. 1: Report one type of psychological distress; 2: Report two type of psychological distress; 3: Report three type of psychological distress; 4: Report four type of psychological distress; 5: Report five type of psychological distress.

mental health of pregnant women. However, cross-sectional nature limits the interpretation of the causal relationship between family support and mental health. Further longitudinal studies about the causal relationship between family support and mental health will be an essential area of future research, which may help to identify appropriate and effective interventions for pregnant and postpartum women to prevent from the mental health problems.

ARTICLE HIGHLIGHTS

Research background

Pregnant women may be more vulnerable to psychological distress during major life-threatening public health events. The spread of the corona virus disease 2019 (COVID-19) is likely to cause greater psychological stress, which may cause extra psychological problems for pregnant women.

Research motivation

The spread of the COVID-19 may cause extra psychological problems for pregnant women. Women who have better supportive networks of family may experience less psychological stress. However, the literatures on the role of family support in maternal psychological distress during the COVID-19 pandemic was limited.

Research objectives

This study aimed to clarify the potential role of family support on psychological distress for women during pregnancy stages at the peak of the COVID-19 epidemic.

Research methods

The authors retrospectively collected socio-demographic variables, information of pregnancy, and information of psychological distress and the perceived family support of pregnant women in China.

Research results

Among 2232 pregnant women, 45.4% women reported having at least one psychological distress during the COVID-19 pandemic. The women who reported having inadequate family support were more likely to suffer from multiple psychological distress than women received adequate family support. Perceived family support was negatively correlated with depressive symptoms, anxiety symptoms, and PTSD symptoms.

Research conclusions

Family support was significantly negatively correlated with psychological distress. Adequate family support has a positive impact on the mental health of pregnant women during the COVID-19 pandemic.

Research perspectives

Adequate family support is important for maternal mental health. Further research is needed to understand the role and mechanism of this factor in order to utilize family support to help pregnant women in major life-threatening public health events.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 375-387

DOI: 10.5498/wjp.v11.i7.375

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Prospective Study

Classification of subtypes of patients with eating disorders by correspondence analysis

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Author contributions: Martín J, Padierna A, and Quintana JM designed the study; Martín J, Padierna A and Berjano B performed the data collection; Martín J and Antón-Ladislao A performed data analyses; Martín J and Padierna A were responsible for manuscript writing; all the authors contributed to interpreting the data; and all authors read and approved the final manuscript.

Supported by the Carlos III Health Institute Project "Adaptation and Validation of the Clinical Assessment Inventory for Eating Disorders", No. PI09/90832.

Institutional review board statement: The study was approved by the Ethics Committee of the Galdakao-Usansolo Hospital.

Clinical trial registration statement: The clinical trial is registered with ClinicalTrials.gov, using identifier NCT02483117. Details can be found at https://clinicaltrials.gov/ct2/show/NCT02483117.

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Abstract

BACKGROUND

Grouping eating disorders (ED) patients into subtypes could help improve the establishment of more effective diagnostic and treatment strategies.

AIM

To identify clinically meaningful subgroups among subjects with ED using multiple correspondence analysis (MCA).

METHODS

A prospective cohort study was conducted of all outpatients diagnosed for an ED at an Eating Disorders Outpatient Clinic to characterize groups of patients with ED into subtypes according to sociodemographic and psychosocial impairment data, and to validate the results using several illustrative variables. In all, 176 (72.13%) patients completed five questionnaires (clinical impairment assessment, eating attitudes test-12, ED-short form health-related quality of life, metacognitions questionnaire, Penn State Worry Questionnaire) and sociodemographic data. ED patient groups were defined using MCA and cluster analysis. Results were validated using key outcomes of subtypes of ED.

RESULTS

Four ED subgroups were identified based on the sociodemographic and psychosocial impairment data.

CONCLUSION

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors of this manuscript having no conflicts of interest to disclose.

Data sharing statement: There is no additional data available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 8, 2021
Peer-review started: February 8, 2021
First decision: March 30, 2021
Revised: April 9, 2021
Accepted: June 16, 2021
Article in press: June 16, 2021
Published online: July 19, 2021

P-Reviewer: Crenn PP
S-Editor: Zhang H

ED patients were differentiated into well-defined outcome groups according to specific clusters of compensating behaviours.

Key Words: Multiple correspondence analysis; Eating disorders; Compensating behaviour; Observational descriptive study

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Core Tip: This is the first study to apply multiple correspondence analysis to eating disorders (ED) diagnostic data and to use cluster analysis (CA) in such detail to search for ED patient groups in this area. Multiple correspondence analysis and CA made it possible to identify different typologies of patients with specific features. Grouping ED patients into subtypes could help improve the establishment of more effective strategies of diagnosis and treatment, and improve patient care and prognosis in clinical practice.

Citation: Martín J, Anton-Ladislao A, Padierna Á, Berjano B, Quintana JM. Classification of subtypes of patients with eating disorders by correspondence analysis. *World J Psychiatr* 2021; 11(7): 375-387
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/375.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.375

INTRODUCTION

Eating disorders (ED) are serious psychiatric conditions; clinical presentations of persons with ED[1,2] vary substantially and they may be associated with many factors, *e.g.*, sociodemographic as gender[3] or clinical as personality profiles[4]. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-5[5] aims to better capture the presentations of ED symptoms observed by modifying previous ED diagnostic criteria. However, as Turner *et al*[6] have, noted some researchers remain concerned, that these adjustments will fail adequately to address the substantial heterogeneity in clinical presentations amongst patients with ED[1]. It is important to research subtypes of ED, since otherwise the field might merely end up 'studying what it defines' (or failing to study anything it does not define)[7]. Thus, removing any reference to non-purging compensatory behaviors would reinforce the impression-(created by subtyping) that bulimic-type ED characterized by purging behaviors is more severe than that involving non-purging behaviors when there is actually little empirical evidence to support this view[7,8]. Insofar as distinct subgroups of ED patients can be reliably identified, it is possible that these groupings might be used to inform assessment, treatment and future diagnostic nosologies[9]. Multiple correspondence analysis (MCA) is an exploratory technique that offers descriptive patterns based on the categories of the original active variables[10,11]. It transforms the information on the categorical active variables into continuous factors. The relative positions of the categories given by the MCA factors are used to perform the cluster analysis (CA) which classifies information into relatively homogenous groups. By combining MCA and CA it might be possible to arrive at a classification of the subjects suggested by the data, rather than defined *a priori*, where subjects in each group are similar to one another but dissimilar to those of other groups[10,12].

Grouping ED patients into subtypes could help improve the establishment of more effective strategies of diagnosis and treatment, and improve patient care and prognosis in clinical practice. The aim of this study was to identify ED patient subtypes. To this end, MCA and CA statistical techniques were combined to analyze clinical data obtained in a prospective cohort study of ED patients treated in an ED Outpatient Clinic. The subtypes were then validated by estimating their relationships to key outcomes such as health-related quality of life (HRQoL), psychosocial impairment due to ED, worry and metacognitions, eating problems, and sociodemographic variables.

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P-Editor: Ma YJ

MATERIALS AND METHODS

Participants

A prospective cohort study was conducted of all patients diagnosed with and treated for an ED at the Eating Disorders Outpatient Clinic The clinic forms part of the psychiatric services at the hospital, which serves a population of 300000. It is part of the Basque Health Care Service, which provides unlimited free care to nearly 100% of the population. Outpatients recruited between January 2010 and January 2011 were considered eligible for the study if they had received a diagnosis of anorexia nervosa (AN), bulimia nervosa (BN), or an ED not otherwise specified (EDNOS) by a psychiatrist, on the basis of the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision[5]. Patients were required to provide written informed consent before participating. They were excluded if they had a malignant, severe organic disease were unable to complete the questionnaires because of languagedifficulties, or had not given their written informed consent to participate in the study.

The study received approval from the institutional review board of the Hospital.

Measures

ED patients gave their sociodemographic data, including age, gender, marital status, education, employment status, and living situation.

The clinical impairment assessment (CIA v.3.0)[13,14] is a 16-item self-report instrument specifically designed to assess psychosocial impairment secondary to features of an ED. A higher score indicates greater impairment. The CIA report of psychometric properties indicated that the measure was both adequate and valid[13,15].

Eating pathologies were measured using the eating attitudes test-12 (EAT-12)[16]. This is a 12-item instrument, which uses a 4-point scale, with scores from 0 (never) to 3 (always). Higher scores indicate more disordered eating. Its validity as a measure of disordered eating has been backed by previous studies[17,18].

The quality of life of ED patients was evaluated using the health-related quality of life in ED-short form)[19] ,a 20-item questionnaire divided into two domains: social maladjustment and mental health and functionality. The lower the quality of life, the higher the score[15,20].

The metacognitions questionnaire (MCQ-30)[21] is a brief multidimensional measure of a range of metacognitive processes and metacognitive beliefs related to worry and cognition relevant to vulnerability to and maintenance of emotional disorders. Higher scores reflect a more dysfunctional metacognitive belief. The subscales have good psychometric properties[21,22].

The Penn State Worry Questionnaire (PSWQ-R) is a 16-item self-report measure of trait worry that is widely used to measure pathological worry[23]. A Spanish version reduced to 11 items was used[24]. Higher scores indicate greater levels of pathological worry. The PSWQ-R has been shown to have good psychometric properties[25,26].

Procedure

Data gathering began in 2010. Psychiatrists who collaborated in the study informed their patients of the aims of the study and recorded sociodemographic information. Patients agreeing participate were mailed questionnaires and an informed consent form ,which they were asked to mail back using an enclosed, pre- franked envelope. Two reminders were mailed out at 15-d intervals to patients who failed to reply to the first mailing.

Statistical analysis

Various multivariate techniques are used in order to synthesize the information contained in a large set of explanatory variables into a few components, also called factors. One of them is the technique selected for this analysis, MCA, which is designed for categorical explanatory variables, while others, as principal component analysis, are designed for continuous variables. Based on the categories of the original variables, MCA provides descriptive patterns by factors. In the continuous factors, therefore, each category of variables is represented by a numerical value and a positive/negative sign, used for interpretation. Graphical displays of these factors are very useful in interpretation, as the association between the categories is indicated by their relative position on the graph. The closer the categories are to one another, the stronger the association. Variables included in the analysis are known as active variables, whilst those not included in the analysis but used to verify the relationship

with active variables are termed illustrative variables or outcomes[10]. A descriptive analysis was made of sociodemographic and psychosocial impairment data, using frequencies and percentages. Means and standard deviations were also used as additional information for questionnaires of psychosocial impairment. The active variables in the MCA were gender, age (13-25, 26-35, 35-63), marital status [single, spouse/partner, divorced/widow(er)], education completed (primary, secondary, higher), employment status (employed, unemployed, student, disabled, unpaid work/housewife), living situation (living alone, with partner/children, friends, parents/siblings), MCQ-30 questionnaire (≤ 57, 58-75, > 75), CIA questionnaire (< 16, ≥ 16), EAT-12 questionnaire (< 8, ≥ 8), HeRQoLED-SocM (≤ 50, > 50), HeRQoLED-MHF (≤ 50, > 50) and PSWQ-R (≤ 28, > 28). Type (AN, BN and EDNOS) and subtype (restrictive, purgative and binge) of ED patients were used as illustrative variables.

For classification purposes, CA organizes information into relatively homogeneous groups based on their values in a range of variables — in this case, based on the factors derived from the MCA. In other words, the objective of the CA is to assign individuals into different groups, in the way that individuals from the same group are similar to each other, but dissimilar from individuals of other groups. The number of groups derived from the CA is selected using the minimum inertia lost method[27].

The association between the active variables and the groups derived from the CA was evaluated using the chi-square test (or Fisher's exact test when expected frequencies were less than 5). The non-parametric Kruskal-Wallis test was used for the scores of the psychosocial impairment questionnaires. In addition, the relationship of outcomes or illustrative variables was evaluated according to the groups obtained from the CA. In order to see the stability of the groups obtained and since we had all the active variables measured at 12 mo of follow up too, the same analysis was replicated with the variables at 12 mo of follow up. Statistical analyses were carried out with R v3.0.2 and SAS 9.4 software (copyright, SAS Institute Inc.). "SAS" and the names of all other SAS Institute Inc. products and services are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, United States.

The study was approved by the Ethics Committee of the Galdakao-Usansolo Hospital. Written consent for participation was obtained. ClinicalTrials.gov Identifier: NCT02483117. All methods were used in accordance with the relevant guidelines and regulations.

RESULTS

A total of 244 patients with ED were invited to take part in the study. Of these, 176 filled out the questionnaires. Early dropouts were largely due to patients failing to consent to participation. The mean of the CIA questionnaire was 19.5 (SD 13.6), which indicates a high level of impairment due to ED.

Results from the MCA showed that 74% of data variability could be explained by two factors, the first primarily associated with the HRQoL and the second with socio-demographic data. Figure 1 shows the map created by the first and second factors. The first factor is represented on the horizontal axis and the second on the vertical axis. Variables that were well-represented in the first factor were: the questionnaires related to psychosocial impairment; eating problems; HRQoL; worry; and metacognitions. Categories located in the positive part (right) of the map included lower values at CIA, EAT-12, HeRQoLED-s, MCQ-30, PSWQ. In contrast, higher values of the questionnaires were in the negative part (left). This axis was defined as "Psychosocial impairment: from high to low".Moreover, the relative position of the illustrative variables on the graph indicates that some subtypes of diagnosis according to compensatory behaviour as well as some subtypes of diagnosis related to DSM-IV-TR classification were well represented by this factor. Indeed, restrictive behaviour (AN, EDNOS) was located in the right side of the axis, whereas purgative behaviour (BN, EDNOS) stood on the left of the axis. The variables that were well-represented in the second factor were socio-demographic variables. Categories such as being male, having a spouse, having secondary studies, being a housewife and living with a partner/children were related to the positive part (top). In contrast, the categories of being single, having higher studies, being a student and living with friends or parents or/and a sibling, were related to the negative part of the axis (bottom). This axis was therefore interpreted as "socio-demographic data". As in the other axis, some categories of the illustrative variables were well-represented by this axis. Purgative AN was located in the negative part, while binge behaviour (only in patients with EDNOS diagnosis) was located in the positive part.

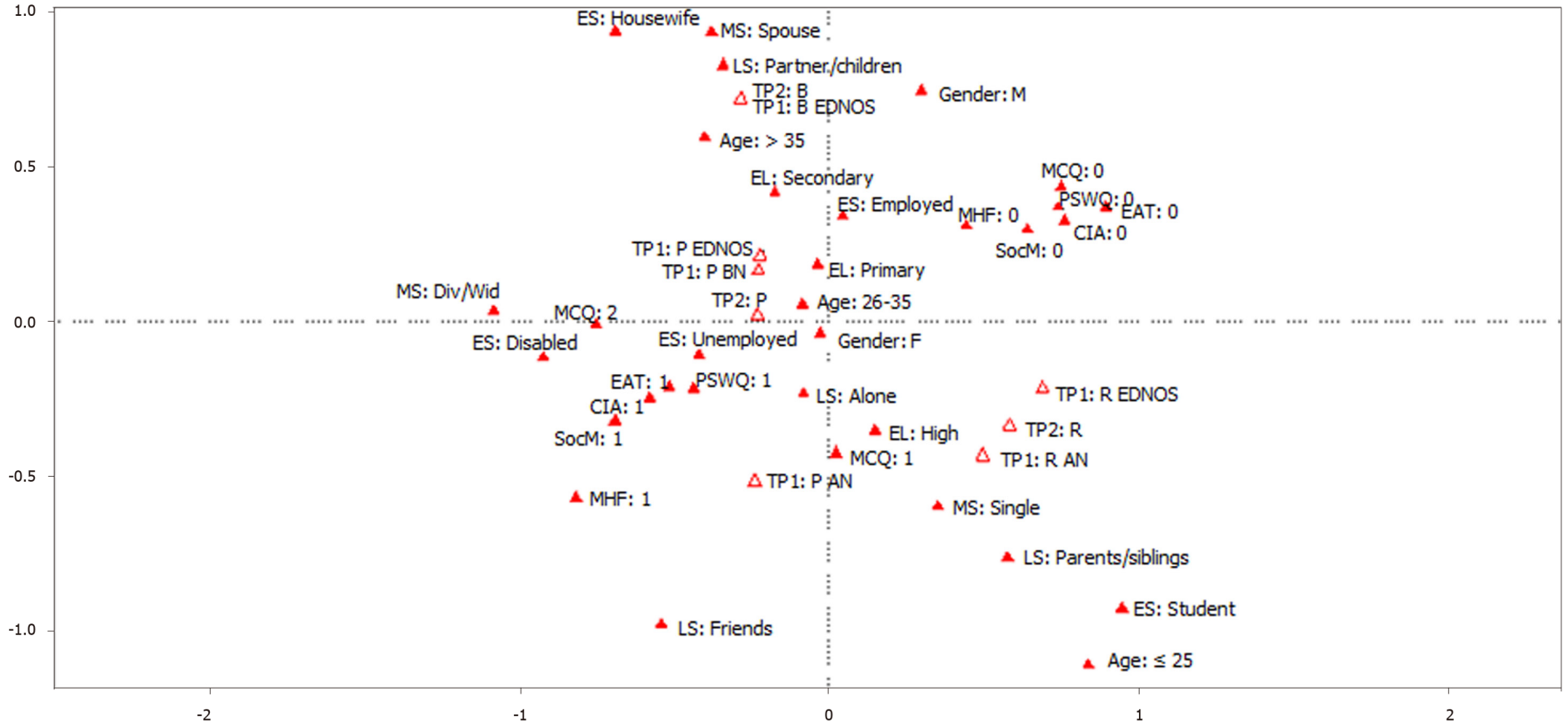


Figure 1 Graphical displays of the two factors/components derived from the multiple correspondence analysis. Active variables (sociodemographic variables). Age (≤ 25, 26-35, > 35); Marital status (single, spouse/partner, divorced/widow(er); Educational level (primary education, secondary education, higher education); Employment status (employed, unemployed, student, disabled, non-paid work/housewife); Living situation (alone, partner/children, friends, parents/siblings). Active variables (questionnaires). Metacognitions questionnaire, (0: ≤ 57, 1: 58-75, 2: > 75). Clinical impairment assessment, (0: ≤ 16, 1: ≥ 16); Eating attitudes test, (0: ≤ 8, 1: ≥ 8). Health-related quality of life in eating disorder-short form, [social maladjustment domain, (0: ≤ 50, 1: > 50); Mental health and functionality domain, (0: ≤ 50, 1: > 50); Penn state worry questionnaire (0: ≤ 28, 1: > 28). Red triangles represent the categories of the active variables. White triangles represent the categories of the illustrative or outcome variables. TP1: B EDNOS: Type of patient 1: Binge-eating disorder not-otherwise specified; TP1: P EDNOS: Type of patient 1: Purgative- eating disorder not-otherwise specified; TP1: R EDNOS: Type of patient 1: Restrictive- eating disorder not-otherwise specified; TP1: P BN: Type of patient 1: Purging-bulimia nervosa; TP1: P AN: Type of patient 1: Purging-anorexia nervosa, TP1: R AN: Type of patient 1: restrictive-anorexia nervosa; TP2: R: Type of patient 2: restrictive; TP2: P: Type of patient 2: Purgative; TP2: B: Type of patient 2: binge; G: Gender; F: Female; M: Male; MS: Marital status; EL: Educational level; ES: Employment status; LS: Living situation; MCQ: Metacognitions questionnaire; CIA: Clinical impairment assessment; EAT: Eating attitudes test; HeRQoLED-s: Health-related quality of life in eating disorder-short form; SocM: Social maladjustment domain; MHF: Mental health and functionality domain; PSWQ: Penn State Worry Questionnaire.

Following application of CA to the factors derived from the MCA, four ED patient types were identified (Figure 2) and labelled from A to D. Types A and C were patients with high psychosocial impairment, while types B and D were patients with

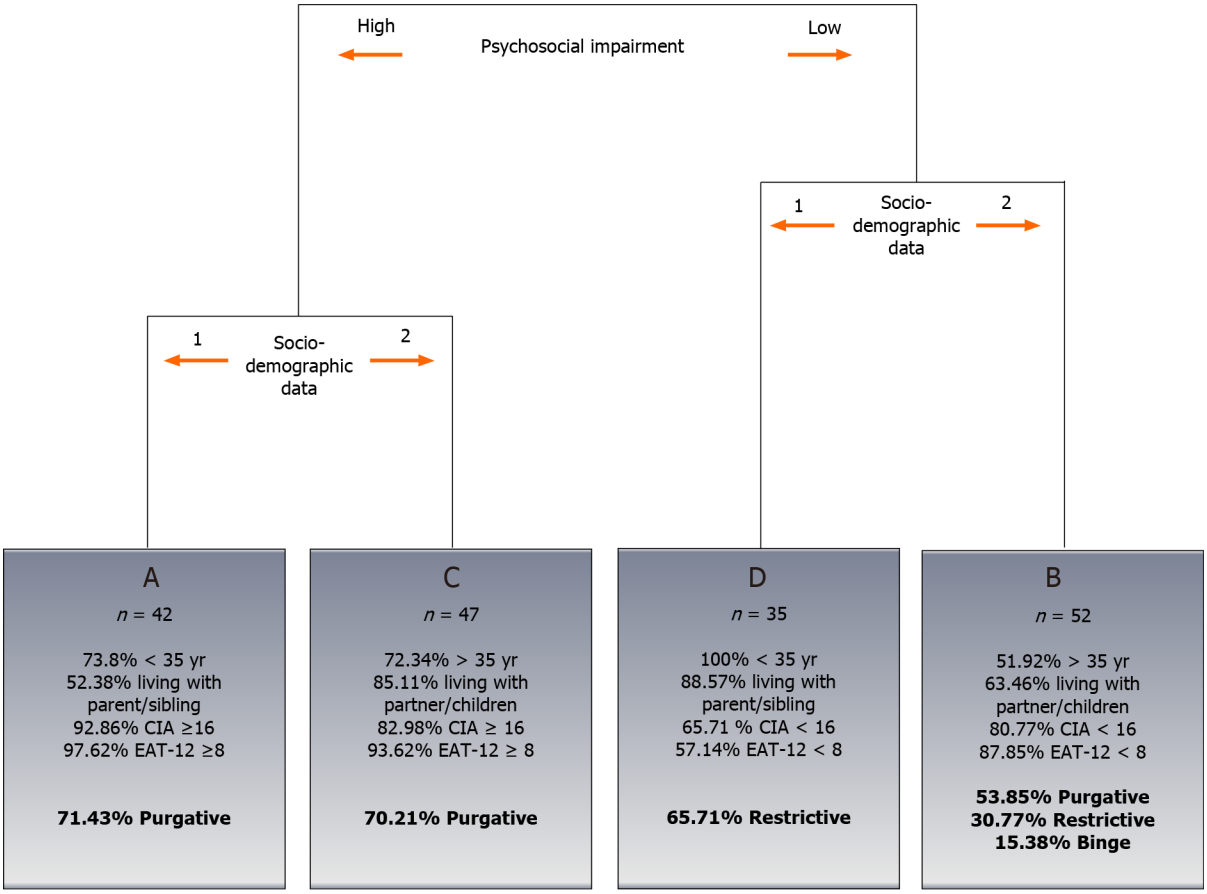


Figure 2 Dendogram obtained from the cluster analysis. The dendogram represents the results from the cluster analysis performed with the two components obtained from the multiple correspondence analyses. The graphical display includes an easy interpretation of the clustering and a brief description of the identified groups. [1]Having < 35 years, being single, having higher studies, being a student and living with friends or parents or/and a sibling; [2]Having > 35 years, being male, having a spouse, having secondary studies, being a housewife and living with partner/children.CIA: Clinical impairment assessment; EAT: Eating attitudes test.

low psychosocial impairment. However, types A and C, and B and D, differed in their socio-demographic characteristics. Figure 3 shows the two-dimensional distribution resulting from graphing the first and second factors. Types were represented by colours and the relative positions of the two illustrative variables were projected on the graph.

Tables 1 and 2 summarize the variables collected for all ED patients across the four ED subtypes. Statistically significant differences between subtypes were observed in all socio-demographic and psychosocial impairment variables, except for gender. Table 2 shows the associations between the subtypes and the illustrative variables and subtypes. Among patients in subtypes A (n = 42) and C (n = 47), 71.43% and 70.21% respectively had purgative behaviours. Subtype D included 35 patients, of whom 65.71% had restrictive behaviours. Among the 52 patients in subtype B, 58.85% had purgative behaviours, 30.77% had restrictive behaviours, and 15.38% had binge behaviours. The distribution of patients across the subtypes was significantly associated with the illustrative variable (P < 0.0001). In order to see the stability of the groups obtained in another way, results at 12 mo of follow-up showed that factors created by the MCA with the 12 mo follow-up data were the same as in the baseline (see material online, Supplementary Tables 1 and 2, Supplementary Figure 1). So, the characteristics that define the groups derived from the CA (A, B, C, D) are stable. Table 3 shows the differences in quality of life among the three groups defined in the literature (AN, BN and EDNOS).

DISCUSSION

The purpose of this study was to identify clinically meaningful subgroups among subjects with ED using multiple correspondence analyses. MCA is a well-established statistical technique that is suitable for suggesting possible diagnostic categories, as

Table 1 Distribution of the active variables related to the patients with eating disorders: Sociodemographic and health-related quality of life variables

	n (%)	Type of patient				*P* value
		A	B	C	D	
Active variables	176	42 (23.86)	52 (29.55)	47 (26.70)	35 (19.89)	
Sociodemographic variables						
Gender (Female)	166 (94.32)	42 (100)	47 (90.38)	44 (93.62)	33 (94.29)	0.25
Age						< 0.0001
≤ 25	42 (23.86)	9 (21.43)	0 (0)	0 (0)	33 (94.29)	
26-35	62 (35.23)	22 (52.38)	25 (48.08)	13 (27.66)	2 (5.71)	
> 35	72 (40.91)	11 (26.19)	27 (51.92)	34 (72.34)	0 (0)	
Marital status						< 0.0001
Single	102 (57.95)	36 (85.71)	26 (50.00)	6 (12.77)	34 (97.14)	
Spouse/partner	64 (36.36)	5 (11.90)	25 (48.08)	33 (70.21)	1 (2.86)	
Divorced/Widow(er)	10 (5.68)	1 (2.38)	1 (1.92)	8 (17.02)	0 (0)	
Educational level						0.007
Primary education	36 (20.45)	7 (16.67)	12 (23.08)	10 (21.28)	7 (20.00)	
Secondary education	56 (31.82)	7 (16.67)	17 (32.69)	24 (51.06)	8 (22.86)	
Higher education	84 (47.73)	28 (66.67)	23 (44.23)	13 (27.66)	20 (57.14)	
Employment status						< 0.0001
Employed	72 (40.91)	20 (47.62)	33 (63.46)	17 (36.17)	2 (5.71)	
Unemployed	25 (14.20)	11 (26.19)	8 (15.38)	6 (12.77)	0 (0)	
Student	41 (23.30)	6 (14.29)	2 (3.85)	0 (0)	33 (94.29)	
Disabled	18 (10.23)	4 (9.52)	2 (3.85)	12 (25.53)	0 (0)	
Non-paid work/housewife	20 (11.36)	1 (2.38)	7 (13.46)	12 (25.53)	0 (0)	
Living situation						< 0.0001
Alone	13 (7.39)	4 (9.52)	5 (9.62)	3 (6.38)	1 (2.86)	
Partner/children	82 (46.59)	8 (19.05)	33 (63.46)	40 (85.11)	1 (2.86)	
Friends	14 (7.95)	8 (19.05)	1 (1.92)	3 (6.38)	2 (5.71)	
Parents/siblings	67 (38.07)	22 (52.38)	13 (25.00)	1 (2.13)	31 (88.57)	
Health-related quality of life variables						
MCQ-30						< 0.0001
≤ 57	59 (33.52)	4 (9.52)	30 (57.69)	7 (14.89)	18 (51.43)	
58-75	58 (32.95)	23 (54.76)	11 (21.15)	10 (21.28)	14 (40.00)	
> 75	59 (33.52)	15 (35.71)	11 (21.15)	30 (63.83)	3 (8.57)	
MCQ-30[1]	67.0 (18.5)	72.2 (12.4)^{BD}	57.6 (18.6)^{AC}	78.4 (18.4)^{BD}	58.6 (12.8)^{AC}	< 0.0001
CIA (≥ 16)	100 (56.82)	39 (92.86)	10 (19.23)	39 (82.98)	12 (34.29)	< 0.0001
CIA[1]	19.5 (13.6)	30.7 (9.6)^{BD}	9.2 (8.0)^{AC}	26.0 (12.8)^{BD}	12.2 (9.2)^{AC}	< 0.0001
EAT-12 (≥ 8)	111 (63.07)	41 (97.62)	11 (21.15)	44 (93.62)	15 (42.86)	< 0.0001
EAT-12[1]	10.7 (7.5)	16.4 (5.9)^{BD}	4.9 (4.6)^{AC}	14.1 (6.2)^{BD}	7.6 (6.2)^{AC}	< 0.0001
HeRQoLED-s						
SocM (> 50)	84 (47.73)	35 (83.33)	4 (7.69)	35 (74.47)	10 (28.57)	< 0.0001
SocM[1]	48.1 (24.0)	63.9 (16.4)^{BD}	29.0 (15.8)^{AC}	63.1 (19.4)^{BD}	36.6 (20.6)^{AC}	< 0.0001

MHF (> 50)	61 (34.66)	28 (66.67)	2 (3.85)	25 (53.19)	6 (17.14)	< 0.0001
MHF[1]	43.5 (21.7)	56.8 (17.8)^{BD}	29.0 (15.2)^{AC}	56.9 (17.8)^{BD}	30.4 (17.0)^{AC}	< 0.0001
PSWQ-R (> 28)	110 (62.50)	38 (90.48)	18 (34.62)	39 (82.98)	15 (42.86)	< 0.0001
PSWQ-R[1]	29.7 (8.3)	34.8 (4.1)^{BD}	24.4 (8.4)^{AC}	33.6 (5.9)^{BD}	25.9 (8.2)^{AC}	< 0.0001

[1]Results showed as mean (standard deviation). Types of patients have been labeled in alphabetical order. The four subtypes (A, B, C and D) identified for the MCA factors "Psychosocial impairment" (first factor), and "Socio-demographic data" (second factor) provide a typology of eating disorders patients. MCQ: Metacognitions questionnaire; CIA: Clinical impairment assessment; EAT-12: Eating attitudes test; HeRQoLED: Health-related quality of life in eating disorder-short form; SocM: Social maladjustment domain; MHF: Mental health and functionality domain; PSWQ-R: Penn state worry questionnaire.

Table 2 Distribution of the illustrative variables, by subtype

	n (%)	Type of patient				*P* value
		A	B	C	D	
Illustrative variables						
Type of ED						0.11
AN	53 (30.11)	17 (40.48)	13 (25.00)	8 (17.02)	15 (42.86)	
BN	34 (19.32)	6 (14.29)	10 (19.23)	13 (27.66)	5 (14.29)	
EDNOS	89 (50.57)	19 (45.24)	29 (55.77)	26 (55.32)	15 (42.86)	
Subtype of ED						< 0.0001
Restrictive	51 (28.98)	8 (19.05)	16 (30.77)	4 (8.51)	23 (65.71)	
Purgative	103 (58.52)	30 (71.43)	28 (53.85)	33 (70.21)	12 (34.29)	
Binge	22 (12.50)	4 (9.52)	8 (15.38)	10 (21.28)	0 (0)	

Types of patients have been labeled in alphabetical order. The four subtypes (A, B, C and D) identified for the MCA factors "Psychosocial impairment" (first factor), and "Socio-demographic data" (second factor) provide a typology of eating disorders patients. ED: Eating disorder; AN: Anorexia nervosa; BN: Bulimia nervosa; EDNOS: Eating disorder not otherwise specified. Type and subtype of eating disorder are based on DMS-IV-TR.

seeks to identify clusters of individuals with similar features. In this study, ED outpatients can be categorized by two main components: one related to sociodemographic data (in graphical terms, shown by the second factor, in which negative values were associated with being old and living with partner/children and positive values were associated with being young and living with parents/siblings), and the other related to psychosocial impairment data (shown by the first factor, in which positive values were associated with better HRQoL and negative values were associated with worse HRQoL). In the hierarchy used, patients were first classified based on HRQoL variables, followed by the sociodemographic variables. The four subtypes (A, B, C, and D) provide a typology of ED patients.

Moreover MCA and CA made it possible to identify different typologies of patients with specific features. Types D and A were similar with regard to sociodemographic data, while Types A and C (D and C) were similar with regard to psychosocial impairment variables. In relation to the sociodemographic variables, Types D and A were characterized by being younger, having a higher education level, being single, and living with their parents or siblings. Types B and C, in contrast, were characterized by being older (> 35 years), having secondary education and living with their partner/children. According to psychosocial impairment variables, Types A and C had the most severe ED and were characterized by higher psychosocial impairment, ED severity, lower HRQoL, higher dysfunctional metacognitive belief and level of pathological worry, while Types D and B had a lower psychosocial impairment and less severe ED. As regards the diagnostic, as in this study, other research[28,29] have also failed to identify specific differences between the HRQoL effect of distinct ED diagnostic groups. With regard to the type of compensating behaviour, 65.71% of patients in Group D, and 53.85% of patients in Group B belong to the group of restrictive patients; while 71.43% of patients in Group A and 70.21% of those in Group C belong to the group of purgative patients.

Table 3 Differences in quality of life among the three groups defined in the literature

	Total	Type of ED			*P* value
	n (%)	AN, *n* (%)	BN, *n* (%)	EDNOS, *n* (%)	
Health-related quality of life variables	176	53 (30.11)	34 (19.32)	89 (50.57)	
MCQ-30					0.25
≤ 57	59 (33.52)	17 (32.08)	8 (23.53)	34 (38.20)	
58-75	58 (32.95)	22 (41.51)	11 (32.35)	25 (28.09)	
> 75	59 (33.52)	14 (26.42)	15 (44.12)	30 (33.71)	
MCQ-30[1]	67.0 (18.5)	65.3 (19.5)	72.1 (18.5)	66.1 (17.7)	0.19
CIA (≥ 16)	100 (56.82)	32 (60.38)	20 (58.82)	48 (53.93)	0.73
CIA[1]	19.5 (13.6)	21.7 (14.4)	21.3 (13.9)	17.6 (12.8)	0.17
EAT-12 (≥ 8)	111 (63.07)	35 (66.04)	22 (64.71)	54 (60.67)	0.8
EAT-12[1]	10.7 (7.5)	12.9 (8.6)	12.1 (8.1)	8.9 (6.1)	0.02
HeRQoLED-s					
SocM (> 50)	84 (47.73)	25 (47.17)	19 (55.88)	40 (44.94)	0.55
SocM[1]	48.1 (24.0)	48.4 (25.2)	52.0 (25.0)	46.5 (22.9)	0.58
MHF (> 50)	61 (34.66)	21 (39.62)	12 (35.29)	28 (31.46)	0.61
MHF[1]	43.5 (21.7)	43.3 (24.5)	44.2 (23.3)	43.4 (19.5)	0.99
PSWQ-R (> 28)	110 (62.50)	32 (60.38)	24 (70.59)	54 (60.67)	0.56
PSWQ-R[1]	29.7 (8.3)	28.6 (8.7)	31.1 (9.0)	29.8 (7.7)	0.23

[1]Results showed as mean (standard deviation). MCQ: Metacognitions questionnaire; CIA: Clinical impairment assessment; EAT: Eating attitudes test; HeRQoLED-s: Health-related quality of life in eating disorder-short form; SocM: Social maladjustment domain; MHF: Mental health and functionality domain; PSWQ: Penn state worry questionnaire; ED: Eating disorders; AN: Anorexia nervosa; BN: Bulimia nervosa; EDNOS: Eating disorder not otherwise specified.

These findings are consistent with those of DeJong *et al*[30], who explored whether purge spectrum groups have a higher degree of clinical severity than restrictive groups. Indeed, a major meta-analysis concluded that vomiting and purgative abuse suggested an unfavourable prognosis[31].

Patients with restrictive subtypes of ED are known to tend to underestimate the impact of their illness on their everyday activities and often continue to work and to maintain an active lifestyle, even at extreme levels of starvation[32]. There is some evidence that individuals with bingeing and/or purging forms of AN are more impaired than those with restrictive AN[30,33]. Several authors have suggested that restrictive EDs are often experienced as ego-syntonic as a result of the highly valued weight loss associated with these disorders[30,34,35]. In the study by DeJong *et al*[30], there were no differences in the CIA scores of different diagnostic groups (AN, BN, EDNOS). However when the groups were divided into restrictive and binge-purge subtypes, significant differences were found, as in this study. This suggests a greater degree of functional impairment amongst binge-purge spectrum diagnoses. This is consistent with an apparently higher degree of clinical severity amongst binge-purge spectrum groups than restrictive groups[30]. As Fairburn *et al*[2] have suggested, is that EDs are not stable. As Fairburn *et al*[36] one possible explanation note, the current arrangement used for classifying EDs is a historical accident that poorly reflects the clinical reality. They propose a (transdiagnostic) model highlighting similarities amongst diagnoses rather than focusing on differences between EDs[36]. Such similarities include extreme dietary restraint and restriction, binge eating, self-induced vomiting and misuse of laxatives, driven exercising, body checking and avoidance, and an over-evaluation of control over eating, shape and weight[37,38].

In DSM-5 the subtypes of BN disappear, since in clinical practice, the non-purging subtype was uncommon and tended to be confused with the diagnosis of binge ED [39]. Although it is important to clarify that fasting and/or excessive exercise are still considered as control behavior in order not to gain weight in BN, so that this type of

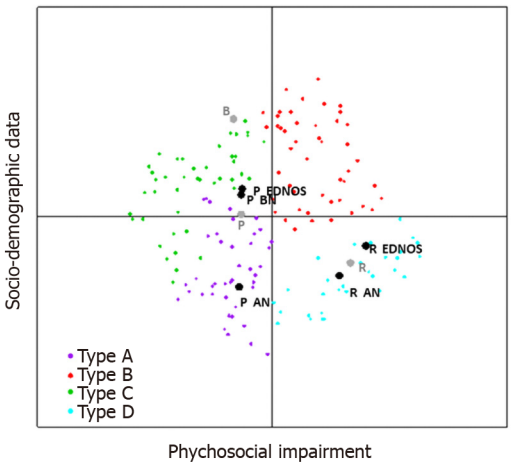


Figure 3 Map created by the first and second factors derived from the multiple correspondence analysis. Black dots in the plane represent the categories of the illustrative variable "subtypes of diagnosis according to compensatory behaviour and Diagnostic and Statistical Manual of Mental Disorders-IV classification". Grey dots represent the categories of the illustrative variable "subtype of diagnosis according to compensatory behaviour". The relative positions of the patients in this plane are represented by different colours, depending on the type derived from the cluster. B EDNOS: Eating disorder not otherwise specified, subtype binge; P EDNOS: Eating disorder not otherwise specified, subtype purgative; P BN: Bulimia nervosa, subtype purgative; P: Purgative; P AN: Anorexia nervosa, subtype purgative; R EDNOS: Eating disorder not otherwise specified, subtype restrictive; R: Restrictive; R AN: Anorexia nervosa, subtype restrictive.

patients could continue to be diagnosed. The main purpose of the DSM is to be clinically useful, *i.e.,* to improve the assessment and care of individuals with mental disorders[39]. The current focus of the DSM on "clinical utility" may incentivize the use of MCA and CA methods; the groups of ED patients formed after applying this methodology, do so based on common characteristics (sociodemographic, clinical and HRQoL), which may or may not coincide with the clinical diagnosis of each patient (DSM criteria). The data of this study may have important implications for ED patient care. The development of compensating behaviour-oriented treatments may prove useful for management of ED patients. But before these findings can be used to justify adjustments in therapeutic interventions, they will have to be replicated using the DSM-5 criteria to examine whether similar, or different clusters are present in different populations. Furthermore, future studies are needed to evaluate our ability to use this CA prospectively to classify disease severity and improve ED control by personalizing ED management. It would be interesting to determine whether the cluster groups have a differential response to one or more specific ED treatments. The potential interest in clinical practice is the usefulness that this method can have for clinicians, detecting typologies that may be useful for decision-making in these types of patients.

Strenghts and limitations

This study has several strengths. The MCA sought to identify groups of patients with homogeneous characteristics. For quality of life, the MCA methodology shows groups that are more discriminating, *i.e.*, patients of each group (A, B, C, D) are more similar/homogeneous among themselves and dissimilar/heterogeneous among the different groups. This methodology has proven useful for eliminating superfluous variables and retaining significant ones[10]. Traditional statistical methods, such as regression models, are designed to test the relationship between explanatory or independent variables and one outcome or dependent variable. In contrast, the aim in this study was to create ED patient typologies that were not strictly related to a specific outcome. The utility of this approach lies in the fact that the classification does not depend on a specific outcome, but is instead related to several[10]. Appropriate validation of the subtypes identified was provided by statistically significant relationships between the subtypes and several key outcomes.

To the authors' knowledge, this is the first study to apply MCA to ED diagnostic data and to use CA in such detail to search for ED patient groups in this area. Based on a review of the existing literature, only one study[40] used MCA in ED patients, but only in AN patients, and for another purpose (the aim was to differentiate patients with AN into well-defined outcome groups according to specific clusters of prognostic factors).

This study has a number of limitations. The first of these is that it only included patients who were attending a dedicated ED outpatient care program. It may therefore not necessarily be possible to extrapolate the results to other settings, such as

inpatients or patients treated as part of primary care. Another limitation is the large number of non-completors, and that there were no analyses of those patients who did and did not participate to determine if they differ based on certain characteristics. The third limitation is that this research was conducted prior to the publication of the DSM-5, and thus used DSM-IV-TR criteria for ED. An examination of patient subtypes across a range of ED patients using the new DSM-5 criteria, will be helpful.

CONCLUSION

In conclusion, four subtypes of ED patients were identified, which were associated with different illustrative variables. The classification was primarily driven by two components: (1) The HRQoL status; and (2) The sociodemographic data. As Fairburn *et al*[37] have noted, a classificatory scheme that reflects the clinical reality would greatly facilitate research and clinical practice.

ARTICLE HIGHLIGHTS

Research background

Eating disorders (ED) pose special problems for patients and have serious implications, including impaired health, psychiatric comorbidity and poor quality of life. Some authors assert that there is heterogeneity in clinical presentations that characterize patients with ED. It is relevant to research subtypes of ED, and these groupings might possibly be used to inform assessment, treatment and future diagnostic nosologies.

Research motivation

This is the first study to apply multiple correspondence analysis to EDs diagnostic data and to use cluster analysis (CA) in such detail to search for EDs patient groups in this area.

Research objectives

The aim of our study was to characterize groups of patients with ED into subtypes according to sociodemographic and psychosocial impairment data using multiple correspondence analysis (MCA), and to validate the results using several illustrative variables and arrive at a classification of the subjects that is suggested by the data, rather being defined *a priori*, where subjects in each group are similar to one another but dissimilar to those from other groups.

Research methods

This study involved ED patients, who were receiving psychiatric care at the Hospital Galdakao-Usansolo in Biscay, Spain, all of whom were informed of the nature of this research by their psychiatrist before agreeing to participate. MCA provides descriptive patterns based on categories of the original variables, and CA organizes information from apparently heterogeneous individuals into relatively homogeneous groups based on their values in different variables.

Research results

Of 176 ED patients were differentiated into well-defined outcome groups according to specific clusters of compensating behaviours. Types D and A were similar with respect to sociodemographic data, while types D and B were similar with respect to psychosocial impairment variables. Types B and D had the least severe ED (according to psychosocial impairment variables); Types A and C had the most severe.

Research conclusions

In our study, the MCA methodology shows groups that are more discriminating, *i.e.*, patients of each group (A, B, C, D) are more similar or homogeneous among themselves and dissimilar or heterogeneous among the different groups. A technique such as MCA synthesizes information on the original variables into a small number of components, making data interpretation easier and more viable.

Research perspectives

Grouping ED patients into subtypes could help improve the establishment of more effective diagnostic and treatment strategies, and improve patient care and prognosis in clinical practice.

ACKNOWLEDGEMENTS

We thank the Research Committee of Galdakao-Usansolo Hospital for help in editing this article. We are most grateful to the individuals with an eating disorder who collaborated with us in our research.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 July 19; 11(7): 388-402

DOI: 10.5498/wjp.v11.i7.388

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Mental health of parents of children with autism spectrum disorder during COVID-19 pandemic: A systematic review

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Author contributions: Yılmaz B, Azak M, and Şahin N contributed to the study design, data collection, and manuscript writing; Yılmaz B and Azak M conducted the data analyses; Şahin N supervised study and made critical revisions for important intellectual content; All authors read and approved the final manuscript.

Conflict-of-interest statement: All authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Children diagnosed with autism spectrum disorder (ASD) may have great difficulties when their routines change, and this may affect the psychological well-being of their parents. For this reason, it is important to examine studies that address the mental health of parents in order to adapt to the coronavirus disease 2019 (COVID-19) pandemic.

AIM

To determine the mental health status of parents with children diagnosed with ASD in the COVID-19 pandemic.

METHODS

The study, which is a systematic review, was conducted between December 15, 2020 and December 30, 2020 by scanning articles in English. The Scopus, Science Direct, PubMed, Cochrane, Web of Science, and Google Scholar databases were used for scanning. The keywords COVID-19 AND ("autism" OR "autistic" OR "autism spectrum disorder") AND parent AND ("mental health" OR "anxiety" OR "stress") were used in the search process. The inclusion criteria in the study were findings regarding the mental health of parents with children diagnosed with ASD in the COVID-19 pandemic, addressing their anxiety and stress situations, being a research article, and accessing the full text of the article.

RESULTS

In the study, a total of 6389 articles were reached, and the full texts of 173 articles were evaluated for eligibility. After the articles excluded by the full-text search were eliminated, 12 studies involving 7105 parents were included in the analysis. The findings obtained from the articles containing data on mental health in the COVID-19 pandemic of parents with children with autism spectrum disorder

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Manuscript source: Invited manuscript

Specialty type: Psychology

Country/Territory of origin: Turkey

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 7, 2021
Peer-review started: February 7, 2021
First decision: March 16, 2021
Revised: March 26, 2021
Accepted: June 3, 2021
Article in press: June 3, 2021
Published online: July 19, 2021

P-Reviewer: Afzal MS, Saad K
S-Editor: Liu M
L-Editor: Filipodia
P-Editor: Wang LYT

were discussed in three groups. These were findings on the experiences of parents with children with ASD in the COVID-19 pandemic regarding the areas where parents with children with ASD need support in the COVID-19 pandemic and methods of coping with the COVID-19 pandemic for parents with children with ASD. In the systematic review, it was determined that the anxiety and stress of the parents increased, they needed more support compared to the pre-pandemic period, and they had difficulty coping.

CONCLUSION
In this systematic review, it was concluded that the COVID-19 pandemic negatively affected the mental health of the parents of children with ASD.

Key Words: Autism spectrum disorder; COVID-19; Mental health; Pandemic; Parents

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Core Tip: Parents with a child diagnosed with autism spectrum disorder (ASD) in the coronavirus disease 2019 (COVID-19) pandemic may have a hard time explaining the COVID-19 pandemic, changes in routines and safety measures to their children in a comprehensible way. Parents may feel stressed and anxious as they have difficulty managing the process and need support in using effective coping methods. It is important to analyze the results of studies on the mental health of parents with children with ASD in the COVID-19 pandemic period. This is the first study to systematically examine the mental health status of the parents of children with ASD in the COVID-19 pandemic period.

Citation: Yılmaz B, Azak M, Şahin N. Mental health of parents of children with autism spectrum disorder during COVID-19 pandemic: A systematic review. *World J Psychiatr* 2021; 11(7): 388-402
URL: https://www.wjgnet.com/2220-3206/full/v11/i7/388.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i7.388

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic and disaster processes significantly adversely affect individuals with severe and chronic mental illness. Data on individuals diagnosed with autism spectrum disorder (ASD), which is one of the most common neurodevelopmental disorders in the world, and their parents' experiences in extraordinary conditions are still limited[1]. The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition defines autism as a pervasive developmental disorder characterized by disturbances in social interaction and communication (difficulty in social-emotional response, inability to use and understand non-verbal communication behaviors, inability to initiate and maintain communication appropriate to the level of development), limited and repetitive behaviors. The prevalence of autism, which causes limitations in performing the daily life functions of the individual with its early symptoms, continues to increase[2]. Autism begins in childhood and affects one in every 160 children in the world[3]. In a study conducted throughout the United States, it was reported that ASD was observed in one of every 54 children[4,5].

The World Health Organization (WHO) declared the COVID-19 epidemic as a global pandemic on March 11, 2020[6]. With the announcement of the pandemic, some restrictions started to be applied in countries. Initiatives to reduce the rate of transmission include behavioral recommendations such as comprehensive and frequent hand washing, maintaining social distance, avoiding in-person contact and wearing a facemask[7]. Groups with special needs have faced bigger problems during the pandemic. Children with ASDs and their parents are among the groups adversely affected by the COVID-19 pandemic[8-10]. The pandemic that caused mental problems even in healthy individuals has caused much more distress in children with ASD, who are extremely sensitive to changes in their routine[11,12]. Children with ASD may

present the psychosocial distress they experience due to the pandemic in the form of aggression, tantrums or refusing to participate in daily activities[8]. Furthermore, children with ASD may have difficulties without training in hand washing, avoiding eye contact, and especially wearing a facemask. The necessity to wear a mask is particularly disturbing for any child who has sensory sensitivity and does not understand the rationale for wearing a mask[13,14].

Parenting a child with ASD may be stressful[15]. Meeting the needs of these children may be more difficult for parents due to the seriousness of their condition and the chronic spectrum, mental health comorbidities, intense interventions that children need and the difficulty of getting services[16]. During the pandemic, disruption in daily routines, difficulty in accessing health services, inability to access private care and the increased anxiety of parents worsen the psychological wellbeing of children and increase their behavioral problems[17]. Parents have a difficult period in management of children with special needs during the pandemic where people are confined to homes. Normally, the burden of parents was shared with care centers, schools and special education centers. Social distancing is placed between caregivers who can support parents in the care process, and individuals who support these parents in care such as grandparents and parents are left alone due to the risk of COVID-19 transmission[18,19]. As the burden of parents increases, their coping capacity may decrease[20]. The parents of children with ASD, who had felt isolated before the COVID-19 pandemic, may feel more lonely and stressed during the pandemic with compulsory social distancing[21].

Parental health and well-being are directly related to the quality of care parents can provide to their children[21]. In the COVID-19 pandemic, international organizations such as WHO, the United Nations International Children's Emergency Fund and the American Academy of Pediatrics have created guidelines to support parents in management of the pandemic and stress management[22-24]. Similarly, Narzisi[12] recommended the parents of children with ASD to explain what COVID-19 is to the child, structure their daily routines according to this process and maintain their connections with educational institutions so that they can have a healthy pandemic process. It is important for parents to be able to explain the pandemic process to their children so that they and their children feel safer. For this reason, parents should be supported in teaching their children social distancing rules[21]. It is very important that the parents of children with ASD receive social support and have access to professional health services in reducing their stress and improving their emotional wellbeing [16,25]. In the COVID-19 pandemic, anxiety and stress situations, needs and coping methods should be determined, as well as mental health conditions in parents with children with ASD.

This systematic review determined the mental health status of the parents of children with ASD in the COVID-19 pandemic.

MATERIALS AND METHODS

This study is a systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol was followed in preparation of the study and the report. In this systematic review, to reduce the risk of possible bias, the processes of literature review, article selection, data extraction and evaluation of article quality were carried out independently by two researchers, each stage was checked in a session with the third researcher, and a consensus was established. In a session where the three researchers were together for carrying out the process in appropriate form and quality, a pilot study was conducted including searching through the PubMed search engine with a keyword (COVID-19, autism, parent) within the scope of the study, selecting an article, extracting data with five research articles and evaluating the quality of the articles. The differences of opinion and information that emerged after the pilot study were resolved through discussion.

Search strategy

The search processes for this systematic review were conducted between December 15, 2020 and December 30, 2020 and updated on 17 March 2021 to include the latest publications in the publication process. The search procedure was achieved by browsing the Web of Science, PubMed (including MEDLINE), Cochrane, Scopus, Science direct and Google Scholar databases using the keywords COVID-19 AND ("autism" OR "autistic" OR "autism spectrum disorder") AND parent AND ("mental health" OR "anxiety" OR "stress"). The list of references of the included studies was

reviewed to access additional studies.

Selection criteria and selection of studies

Inclusion and exclusion criteria: The articles in English, which could be accessed in full text without any limitation of publication year and country, were included in the study. The systematic review was created according to the PICOS strategy. Participants: the parents of children with ASD; Interventions: effects of the COVID-19 pandemic on mental health; Comparators: the parents of children without ASD; Main outcomes: anxiety, stress, difficulty in coping, loneliness, inadequacy of support systems, social isolation, change in routines and financial difficulties; Additional outcomes: exercise at home, practicing yoga and meditation, reading newspapers, getting support from a therapist, cooking meals, talking to their loved ones on online platforms during the pandemic. These results have been reported in studies and included and presented in this systematic review.

Studies suitable for this systematic review were included based on the following inclusion criteria. In the COVID-19 pandemic, the findings related to the mental health of parents with children with ASD and the anxiety and stress situations they experienced were handled, being a research article, the publication language was English, and the full text of the article was available. Studies with an unknown method and those dealing with the experiences of children with ASD in the COVID-19 pandemic were excluded.

Identification and selection of the studies were achieved independently by two researchers (Yılmaz B, Azak M) in accordance with the inclusion criteria. After repetitive studies were removed from the search results, selection was made according to the title, abstract and full text, respectively. The selection process followed in the systematic review is given in Figure 1.

Data extraction

A data extraction tool developed by the researchers was used to obtain data in the study. With this data extraction tool, data about the authors of the studies and the publication year, research type, method, sample size, number of cases, the country in which the data were collected, the year the data were collected, the data collection instrument and the main results were obtained.

Evaluation of methodological quality

The methodological quality of the articles included in this systematic review was evaluated by one of the researchers and checked by the other two researchers. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement[26] was used to evaluate the quality of the observational (descriptive, cross-sectional and case-control) studies, and the "Critical Appraisal Skills Program: Quality Appraisal Criteria for a Qualitative research" (CASP) was used for qualitative research (https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist-2018.pdf). The STROBE Statement is a checklist of 22 items that indicate the sections that should be written in the article during the preparation of observational research articles. CASP is a form consisting of 10 items that may be used to evaluate the quality of qualitative research.

Data analysis

The narrative synthesis method was used in the analysis of the data. Narrative synthesis is a method that may be used to synthesize both quantitative and qualitative studies, and it can be used when the findings of studies included in the systematic review are not similar enough for meta-analysis[27]. The pattern, data collection methods and data collection instruments of the studies examined in this systematic review were different. Therefore, the findings are presented with the narrative synthesis method.

Ethical aspect of research

In the study, the research articles included in the sample did not require ethics committee approval because they were obtained from accessible electronic databases and search engines. All stages of the study were carried out in accordance with the principles in the Declaration of Helsinki.

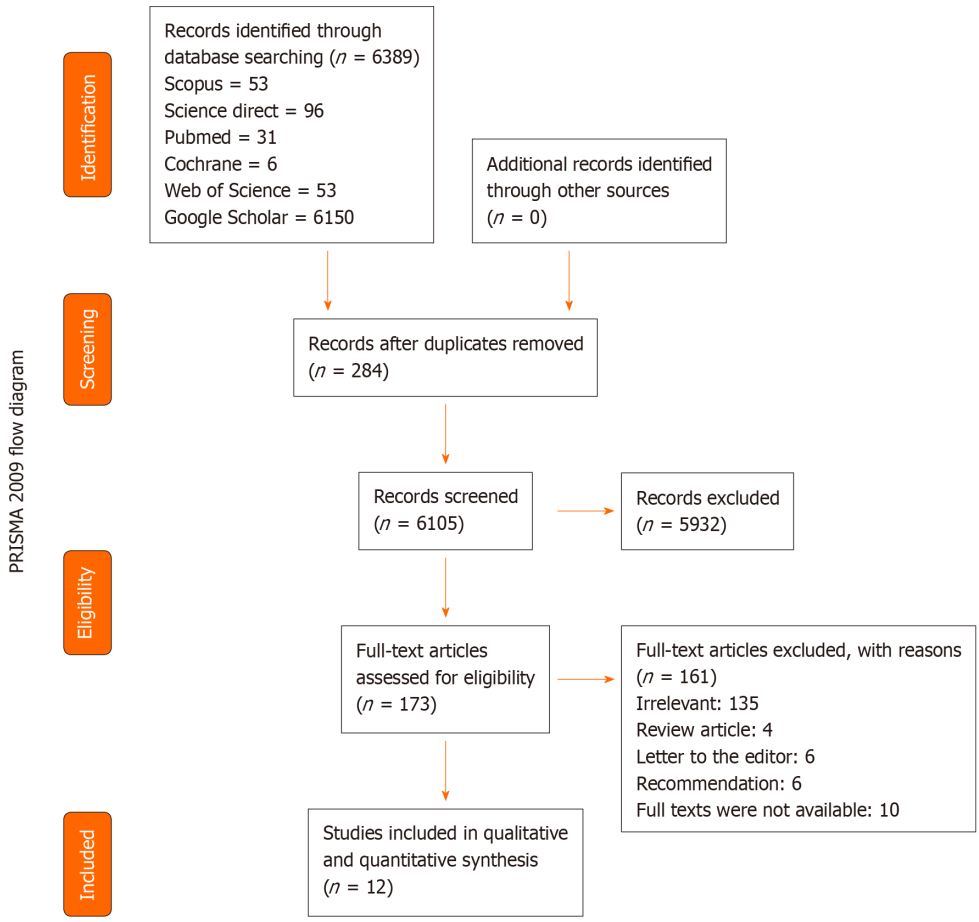


Figure 1 PRISMA flow diagram.

RESULTS

Scanning results

As a result of the search, 6389 records were initially reached. As a result of the examination made according to the title, abstract and full text, respectively, 173 articles were reached. Repetitive records were removed, and data extraction was performed with twelve studies after the examination according to the inclusion criteria. Explanations about the selection process of the articles are shown in Figure 1. In this review, twelve studies that met the inclusion criteria were analyzed, and Table 1 shows the country, type, sample characteristics, data collection instruments and main results of these studies. A total of 12 studies were included in a quantitative and qualitative design (cross-sectional descriptive: 8; comparative cross-sectional descriptive: 1; cohort study: 1; quasi-experimental design: 1; qualitative design: 1). A total of 7105 parents who have children with a diagnosis of ASD were enrolled in the studies that were included in this study. The included studies were carried out in United States, China, Spain, Italy, Saudi Arabia, Portugal and Turkey. While the quantitative research data included in the study were collected through online questionnaires, the qualitative research data were obtained by phone call *via* semi-structured forms.

Methodological quality assessment results

When the reporting quality of the observational studies was evaluated over 22 points with the 22-item STROBE, the mean score was found to be 19.54 (range: 17-22). In the evaluation of qualitative research using CASP, it was found that the quality score was 9.0 (Table 1). While disasters and epidemics affect the whole society negatively, they affect individuals with ASD in the disadvantaged group and their parents mentally. In the systematic review, the results obtained from the articles containing data on the mental health of parents with children with ASD in the COVID-19 pandemic were discussed in three groups. These were results regarding the experiences of parents with children with ASD in the COVID-19 pandemic, results regarding the areas where parents with children with ASD need support in the COVID-19 pandemic and

Table 1 Summary of the studies included in this systematic review

Ref.	Country	Research type	Data collection instrument	Sample	Main results	Critical appraisal toll
Alhuzimi [28], 2021	Saudi Arabia	Cross-sectional descriptive	Demographic Form The Parent Stress Index-Short Form The General Health Questionnaire	150 parents of children with ASD	While 94% of the parents reported that their stress levels increased in the COVID-19 pandemic, 78.7% of them reported that the pandemic negatively affected their emotional well-being. The parents stated that the support they received from their relatives during this process reduced their stress levels, fatigue and improved emotional their wellbeing	19/22 STROBE
Althiabi [34], 2021	Saudi Arabia	Cross-sectional descriptive	Demographic Form The General Health Questionnaire The Hospital Anxiety and DepressionScale The Family Impact Questionnaire	211 parents of children with ASD	The parents reported that, in the COVID-19 pandemic, they had difficulty calming their children due to changes in routine and experienced fear and anxiety. They reported that they had difficulties in finding activities and games to keep their children entertained at home. During this process, the parents reported that they sought help from their friends, teachers, doctors and psychologists	21/22 STROBE
Amorim *et al* [29], 2020	Portugal	Comparative, cross-sectional descriptive	Questionnaire form created by researchers	43 parents of children with ASD and 56 control group participants (parents of children without neurodevelopmental problems)	In the study, it was determined that the parents of children with ASD had higher anxiety levels than those with healthy children. The parents reported that they felt tired during the pandemic as they had to spend extra time on their children with ASD. In the study, 55.8% of the parents of children with ASD and 29.6% of the control group reported that the pandemic had a negative effect on emotion management. Social isolation, inability to spend time outside, sudden changes in routines, boredom and distance education practices were reported as the most difficult areas for parents. The parents stated that they frequently talked to their families, close friends, colleagues, and some parents received support from a therapist	17/22 STROBE
Bent *et al* [31], 2020	China	Qualitative	Interview formcreated byresearchers	15 parentsofchildren withASD	The parents had trouble explaining COVID-19 and safety measures to their children. Sudden changes in routines increased children's crying spells and aggression. The parents had difficulty coping with these behavioral problems and adapting to e-learning. The participants reported that they exercised, practiced yoga, meditation, prayed, read newspapers and talked with their close friends online during this period.	9/10 CASP
Colizzi *et al* [30], 2020	Italy	Cross-sectional descriptive	40-question questionnaire created by researchers	527 parents of children with ASD	The parents reported that having a single child, the inability of the child with ASD to speak, the male gender of the child and a single parent having the child's responsibility were among the factors increasing their stress during the pandemic. 19.1% of the parents reported that they received support from a neuropsychiatrist due to the onset of new behavioral problems in their children and due to feeling helpless. The sudden curfew restrictions caused stress for the parents and their children. 47.4% of the participants stated that they needed more health services during the pandemic, 30% needed to strengthen their home support systems, and 16.8% needed more state support in quarantine	18/22 STROBE
Liu *et al*[36], 2021	China	Quasi-experimental	The Self-rating Anxiety Scale The Self-rating Depression Scale The Parenting Stress Index-Short Form	125 mothers having children with ASD	With web-based support, it was found that the mothers' stress and anxiety levels decreased in the COVID-19 pandemic period. The parents reported feeling relaxed as the program facilitated parent-child interaction	20/22 STROBE

			The Herth Hope Index			
Lugo-Marín *et al*[33], 2021	Spain	Cross-sectional descriptive	The Child Behavior Checklist The Symptom Checklist 90 Revised	104 children with ASD, their parents and caregivers	In the data collected 8 wk after the lockdown onset, it was observed that there was an increase in somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism in the parents	21/22 STROBE
Manning *et al*[32], 2020	The United States of America	Cross-sectional descriptive	Questionnaire form created by researchers	474 parents of children with ASD	It was determined that the children with ASD and their parents experienced high levels of stress and fear during the pandemic. The children who had to spend a long time at home exhibited aggressive and problematic behaviors, causing more stress in their parents and making it difficult to cope. 54.5% of the participants stated that they were worried about their children being at home all the time, 52.1% were afraid that they or their children could be infected with COVID-19, and 30.7% stated that they experienced stress due to economic problems. The parents reported that they received the most support from family, friends, school guidance, therapy center and parent support group, respectively, during the pandemic.	18/22 STROBE
Mumbardo-Adam *et al* [35], 2021	Spain	Cross-sectional descriptive	A semi-structured online survey	47 individuals with ASD and parents	The parents reported that they developed new strategies to better manage quarantine with their children with ASD. During this period, 36.2% of the parents reported that they communicated with their relatives online, and 23.4% received online psychological support	20/22 STROBE
Mutluer *et al* [17], 2020	Turkey	Cross-sectional descriptive	Sociodemographic FormThe Beck Anxiety Inventory (for parents) The Aberrant Behavior Checklist (for children) The Pittsburgh Sleep Quality Index (for children)	87 individuals with ASD and parents	The parents reported that children with ASD felt under house arrest because they had difficulty obeying social distancing rules and did not want to wear masks. The participants stated that their children's sleep patterns were disturbed during the pandemic, and they also had sleep problems. The majority of the parents said they could not continue distance education and needed support in this regard. It was determined that 25% of the parents had minimal anxiety, 29% had mild anxiety, 21% had moderate anxiety, and 25% had severe anxiety. The parents reported that they provided each other rest breaks when there was more than one adult at home who could take care of the child with ASD	17/22 STROBE
Wang *et al* [37], 2021	China	Cross-sectional descriptive	Sociodemographic Form The COVID-19 Questionnaire The Connor-Davidson Resilience ScaleThe Simplified Coping Style Questionnaire The Self-Rating Anxiety Scale	1764 parents of children with ASD and 4962 parents of typically developing children	It was found that the parents of children with ASD had more deterioration in their diet, less physical exercise, less social support, higher levels of psychological stress, anxiety and depression, and worse coping strategies than the parents of children with normal development	22/22 STROBE
White *et al* [38], 2021	The United States of America	Cohort study	Brief Family Distress Scale	3502 parents of children with ASD	80% of the parents reported disruptions in their children's special education. 64% of them stated that these disruptions had severely or moderately impacted their children's ASD symptoms, behaviors or challenges. Increasing distress and stress negatively affected their lives	22/22 STROBE

ASD: Autism spectrum disorder; COVID-19: Coronavirus disease 2019.

methods of coping with the COVID-19 pandemic for parents with children with ASD.

Results on the experiences of parents of children with* ASD *in the COVID-19 pandemic

The COVID-19 pandemic affected the parents of children with ASD mentally. In the study conducted in Saudi Arabia, 94% of the parents reported that their stress levels increased, while 78.7% stated that the pandemic affected their emotional wellbeing negatively[28]. Amorim *et al*[29] found that parents with children with ASD had higher anxiety levels than those with healthy children. Colizzi *et al*[30] reported that having a single child, the child with ASD not being able to speak, the child with ASD being male and a single parent having the child's responsibility were among factors that increased stress in the parents. Curfew restrictions that emerged suddenly during the pandemic caused stress in parents and children. Bent *et al*[31] stated that parents had difficulty explaining the restrictions and security measures to their children. The parents reported that their children had difficulty in obeying the social distancing rules, they could not take their children to the market, *etc.* because they did not want to wear a mask and felt under house arrest[17,31]. In the study by Manning *et al*[32], 54.5% of the participants stated that they were worried about their children being at home all the time, 52.1% were afraid that they or their children could be infected with COVID-19, and 30.7% reported that they had stress due to economic difficulties. In Spain, it was observed that there was an increase in somatization, obsessive behavior, depression, anxiety, hostile behavior, paranoid ideas, phobic anxiety and aggression in the parents according to the data collected 8 wk after the start of the lockdown[33].

For individuals with ASDs, changes in their routine may be very disturbing and challenging. It was reported that this situation led to serious behavioral disorders such as crying episodes, increase in aggression and rejection of transition[31]. In the study by Amorim *et al*[29] the mean anxiety score (8.75 ± 0.96) of parents with a child with ASD in the COVID-19 pandemic was found to be significantly higher than the mean score of parents with healthy children (5.36 ± 2.71). Althiabi[34] also reported that the stress levels of parents increased, and they had difficulty in maintaining their mental wellbeing. Children's adaptation levels affect the parents' anxiety. It was determined that children who could continue their routines (7.72 ± 1.84) had significantly higher levels of adaptation than those who could not (5.25 ± 2.75). In the same study, the parents reported that they felt helpless because there was not enough time to change routines. In the study, some parents reported that their children adapted to the situation without any major problems and thought of this process as a school holiday. The majority of parents, on the other hand, stated that other children had to continue their education in the home environment due to the pandemic, and they were tired of housework. One of the changing routines during the pandemic is that e-learning has been placed at the center of life. Parents reported that they felt tired as they had to spend extra time on their children with ASD during the pandemic. Parents revealed that they felt lonely and bored as they had to assume the role of educators during the pandemic. Some participants stated that their children who spent more time at home during the pandemic felt better as they took more responsibility in housework. In another study, 40.4% of the parents reported that they could spend more time with their ASD-diagnosed children, and 31.9% calmed their children by creating school-related activities[35]. In the study by Mutluer *et al*[17] parents stated that their children's sleep patterns were disturbed during the pandemic, and they also had sleep problems. In the study by Amorim *et al*[29], 55.8% of the parents of children with ASD and 29.6% of the control group reported that the COVID-19 pandemic had a negative effect on emotion management. The most difficult areas for parents were expressed as social isolation (41.4%), not being able to spend time outside (13.1%), sudden changes in routines (11.1%), boredom (9.1%) and distance education practices (7.1%). In the quasi-experimental study by Liu *et al*[36] in two sessions per week for 12 wk, relaxation-muscle exercises, home activities with the child, protection strategies, emotional management, parental stress coping strategies and psychological counseling strategies to cope with the pandemic situation were used. With web-based support, it was found that mothers' stress and anxiety levels decreased in the COVID-19 pandemic period. The parents reported feeling relaxed as the program facilitated the parent-child interaction. In a study conducted in China, it was found that the parents of children with ASD had more deterioration in their diet, less physical exercise, less social support, higher levels of psychological stress, anxiety and depression, and worse coping strategies than the parents of children with normal development[37].

Results regarding the areas where parents of children with ASD need support in the COVID-19 pandemic

Parents stated that they had difficulties during the COVID-19 pandemic due to deficiencies in support systems[30]. In the study conducted in Italy, it was reported

that parents with children with ASD needed local health service support, supportive training for e-learning and decrease in quarantine restrictions during the COVID-19 [30]. In the study conducted in Saudi Arabia, it was found that the support that parents received from their relatives reduced parental stress, fatigue and contributed to improving emotional wellbeing[28]. In the study conducted in Turkey, the majority of parents reported that they could not continue distance education and needed support. In the same study, it was determined that 25% of the parents had minimal anxiety, 29% had mild anxiety, 21% had moderate anxiety, and 25% had severe anxiety according to the Beck Anxiety Inventory[17].

In the study conducted in Portugal, 13% of the parents stated that they took their children to a specialist psychologist, and 1.5% of them visited emergency health services at the moment of their children's tantrums[29]. In the study conducted in Saudi Arabia, parents reported that their children with ASD mostly experienced problems in maintaining their care skills, coping with tantrums, controlling their negative behaviors and maintaining communication with their children. Additionally, the parents stated that they needed psychological and financial support the most, respectively[34]. In the study conducted in the United States, it was observed that tele-health services were insufficient in meeting the education and treatment needs of the children of parents. In the study, most of the parents of children with ASD stated that they had difficulty coping with the increasing negative behaviors of their children, and distress and stress negatively affected their lives[37].

In the study conducted in Italy, it was found that 19.1% of parents visited a neuropsychiatrist due to the onset of new behavioral problems in their children and feeling helpless[30]. It was stated by 47.4% of the participants that they needed more health services during the pandemic, 30% needed to strengthen their home support systems, and 16.8% needed more state support in quarantine. It was stated by 25% of the parents that one of the parents had to quit their job (26.1% of mothers, 27.5% of fathers) to take care of their children with ASD. The majority of the participants (94%) stated that this situation was financially difficult for them. During the pandemic, only 27.7% of the parents reported that they could get support from local health services. It was specified by 23% of the parents that they had difficulties in regulating the eating behaviors of their children, 31% had difficulties in providing authority to their children, 78.1% had difficulties in making use of spare time, and 75.7% had difficulties in having their children do homework[30].

The coping methods of parents with children with ASD with the COVID-19 pandemic

The parents of children with ASD resorted to various coping methods in the COVID-19 pandemic process. In the study by Bent *et al*[31], it was found that parents exercised at home, practiced yoga and meditation, read newspapers, cooked meals, talked to their loved ones on online platforms and spent time (bathing, nail care and online shopping) during the pandemic. In the study of Mutluer *et al*[17], it was reported that parents provided each other with rest breaks when there was more than one adult at home who could take care of the child with ASD. In the study by Amorim *et al*[29], it was determined that parents frequently talked to their family, friends and colleagues by video, and some of them received support from a therapist. In another study, it was observed that parents received the most support from their families, friends, school guidance services, therapy centers and parent support groups, respectively, during the pandemic process[32]. In the study conducted in Saudi Arabia, most parents reported that they received online counseling and guidance services to deal with the child's behavior at home and tantrums[34]. In another study, 36.2% of parents stated that they communicated with their relatives online, 23.4% received online psychological support, and 6.4% occasionally walked with their children[37].

DISCUSSION

This study is the first systematic review aimed at determining the mental health status of the parents of children with ASD in the COVID-19 pandemic. The systematic review showed that the difficulties associated with the COVID-19 pandemic negatively affect the mental health of the parents of children with ASD. Restriction of face-to-face education, social activities, and child monitoring during the pandemic process threaten the physical and mental health of children. Parents worldwide are concerned about how to support their children best under these difficult conditions[8-10]. The distinctive features of the diagnosis of ASD put children with ASD and their parents at risk of more adverse effects from the COVID-19 pandemic. Since these children may

have difficulties in social communication, they can develop when they are in environments that support their social interactions[38]. Although regular physical activity may provide a calming and regulating effect on children, they lack this opportunity due to the pandemic[8]. Considering all of these effects on children diagnosed with ASD, the inability of parents, who are deprived of support during the pandemic process, to maintain their mental health becomes prominent. Parents often experience mental distress as they postpone their own needs for their children with ASD and their families[21]. Disruption in healthcare support or services is an additional stressor on families with a child or dependent with ASD during an already stressful time because of the COVID-19 pandemic[39]. Restrictive social and economic regulations, discomfort caused by COVID-19, fear of transmission, isolated family life, closure of schools, lack of support programs for parents, loss of loved ones, work from home and the resulting increase in full-time childcare and home responsibility, as well as financial difficulties, are the main problems that parents experience in this process [8,17,28-32,39,40]. There has been a consensus on this issue in the studies included in this systematic review[17,28-37,39].

Sleep problems significantly affect children with ASD[41]. Studies on children with ASD reported that sleep problems lead to symptoms such as social withdrawal, anxiety and depression and behavioral problems such as self-aggression, hyperactivity, aggression and high levels of irritability during the day[42,43]. Another study noted that disruption in the circadian sleep rhythm increased the symptoms of ASD[44]. All of these effects of sleep problems negatively influence parents, causing an increase in the burden of these parents and an increase in their stress levels. In a study, it was determined that the situation of being home during the pandemic process caused sleep problems in children with ASD, and this situation increased the severity of ASD symptoms[45]. In the study conducted in Italy, it was reported that more behavioral problems were observed during the COVID-19 pandemic process, and these problems were associated with sleep[17]. The occurrence of these problems creates a sense of loss of control in parents and increases their stress[45]. All of these changes in the lives of parents and children also hinder the physical and cognitive development of the child. Therefore, it is clear that there is also an increase in parental stress levels during a pandemic that directly affects children's quality of life[46]. In a study, it was reported that, during the COVID-19 pandemic process, the parents of children with ASD experienced higher levels of anxiety about themselves and their children in comparison to the parents of children without neurobehavioral disorders [29,37]. Similarly, in the study by Alhuzimi[28] it was emphasized that the parents of children with ASD have higher stress levels and lower welfare levels. Manning *et al* [32] stated that children with ASD and their parents experienced high levels of stress during the pandemic process and reported that there were disruptions in their daily life routines. In this process, the issues regarding which they experienced the most stress were related to illness, isolation and materiality[32]. The fear of getting infected in the event of a pandemic is significant in the parents of children with ASD, and this fear increases stress significantly[47]. This was supported by the findings of the study by Manning *et al*[32] on the COVID-19 pandemic. Although staying at home during the isolation process and the obligation to quarantine are measures taken to reduce the transmission of COVID-19, harmful effects of social isolation on the mental health of children and parents may be observed[48]. This may further increase stress in children diagnosed with ASD and their parents[29,30,32]. Lugo-Marín *et al*[33] reported that there was an increase in somatization, obsessive behavior, depression, anxiety, hostile behavior, paranoid ideas, phobic anxiety and aggression in parents in 2 mo after the lockdown onset. Interruptions in the care process are an important need in the parents of children with ASD[49] and have an important role in reducing stress for the parents of children with ASD[50]. However, the decrease in the support received from caregivers during the isolation process and the fact that parents have taken on the entirety of the care burden have made it difficult for these parents to cope. Parents had difficulties in regulating their children's eating behaviors, providing authority to their children, making use of spare time and finding activities, and having their children do homework, and they felt lonely[30,34,35]. In the studies included in the systematic review, it was reported that, in order to cope with this situation, parents had rest breaks when there was another adult at home who could take care of their children with ASD[17,31].

An increase in the severity of ASD symptoms in children has an important role in affecting the stress and wellbeing levels of parents[51-54]. The COVID-19 pandemic process have caused more intense and more frequent behavioral problems in children with ASD[30]. In the study by Manning *et al*[32] one of the studies included in the systematic review, it was reported that the increasing severity in the symptoms of

children with ASD along with the pandemic caused an increase in the stress reported by parents. Children who are confined at home exhibit aggressive and problematic behaviors, causing more stress for their parents and making it difficult to cope. In other studies supporting these results, the pandemic and the increasing behavioral changes in children with ASD were found to play a significant role in the increase of stress in parents[17,30]. Parental stress also reportedly had an effect on emotional well-being[28]. In this sense, there has been a consensus that there is a lack of support for children and parents.

The positive attitude of parents during the COVID-19 pandemic is necessary for them to manage their stress and also control their children's behavior at home[34]. Pottie and Ingram[55] pointed out the importance of social support in helping a parent with a child with ASD cope with stress and raise their mood. All kinds of support from the community and from parents who experience similar situations facilitate the home care processes of children with ASD and their parents[56]. For this reason, during the pandemic, it is necessary to maintain contact in online environments with all individuals and institutions that parents can receive support from such as other parents, teachers, therapists and health professionals who experience similar situations [12]. In a qualitative study, parents stated that, although they could not get together with other parents who were in the same situation during the pandemic, they supported each other in home care through groups established *via* online messaging applications and mentioned how this helped them[57]. Similarly, in the studies included in the systematic review, parents reported that they frequently made video calls with their families and friends[29,31]. Althiabi[34] found that parents sought support from teachers, family members and therapists to take care of their children with ASD during the pandemic outbreak. Bent *et al*[31] stated in their study that it is important to seek help from friends, family, co-workers, therapists and healthcare professionals, as parents must remain strong for their families and children. With the closure of schools, parents are struggling to find different activities at home to support the development of their children with ASD and prevent their symptoms from appearing[57]. In the studies included in the systematic review[30,31,34,35], in accordance with the literature, parents stated that they sought daily activities and events that their children enjoyed. All family members including parents who leave their jobs or work from home due to the pandemic and children whose schools are closed are at home all together. In this process, the support of all family members for each other in the care of the child with ASD also provides a significant reduction in their burden of care[57].

Children diagnosed with ASD can only survive the pandemic with healthy parents. Therefore, parents should take care of their health, both for themselves and their children. Firstly, parents should not disrupt their physical care with adequate nutrition and rest and accept the emotional burden they experience. They should practice spiritual self-care by planning an activity they enjoy. Parents should be encouraged to plan activities they can do with their children in the home environment. Moreover, they should be encouraged to seek help from healthcare professionals when they feel they have mental problems that they cannot cope with[21]. Consistent with the literature, Bent *et al*[31] reported that parents spend time with activities such as bathing, nail care and online shopping as a method of coping with stress. In the qualitative study, the parents stated that they used methods such as walking, cycling, yoga, meditation, reading a newspaper and praying to cope with stress during the COVID-19 pandemic[31]. With the web-based support program prepared by Liu *et al* [36] relaxation-muscle exercises, home activities with the child, protection strategies, emotional management, parental stress coping strategies and psychological counseling strategies to cope with the pandemic situation were implemented. Their study stated that mothers' stress and anxiety levels decreased, and parents reported feeling relaxed as the program facilitated parent-child interaction.

Limitations

The limitations of this study were that studies whose full texts were not available and those published in languages other than the English language were not included in the systematic review, 12 databases were searched, and the gray literature was not screened. Since the pandemic has only the last year, studies in the field are limited. Therefore, the results should be interpreted with caution, as the systematic review was performed with a limited number of descriptive studies (twelve articles) with lower levels of evidence.

CONCLUSION

The COVID-19 pandemic has negatively affected the mental health of children with ASD and their parents. While many factors play a role in increasing the stress levels of parents, stress may also lead to different problems. In this case, it is possible for children with ASD to continue their lives in a healthy way with mentally healthy parents. In the systematic review, it was concluded that parents with children with ASD had difficulty with their children being at home all day long and financial difficulties as they had to quit their jobs. The parents were also able to devote less time to themselves during this process, and their stress and anxiety levels increased. During the pandemic where face-to-face services are interrupted, governments and relevant institutions should provide support for parents with children with ASD, and institutions that provide support should also work to improve the quality of the support they provide. In this process, it may be recommended to research new ways such as online health monitoring, online diagnosis systems, support groups for children and parents, increased tele-health services, tele-therapies and e-health support. Additionally, after the restrictions imposed by the pandemic are removed, it is important to support children with ASD and their parents while they are getting used to their social lives. Support services, such as counseling and helplines, may be created to help parents share their concerns and receive assistance in dealing with specific situations. Parents should be evaluated in terms of mental health, and professional help should be provided for individuals who need support.

ARTICLE HIGHLIGHTS

Research background

Although staying at home prevents the spread of coronavirus disease 2019 (COVID-19), this poses a number of challenges, especially for children with special needs such as autism spectrum disorders (ASD) and their parents. The parents of children with ASD participate in special education practices that involve physical activity in order to cope with the behavioral, cognitive and mental problems of their children. However, during COVID-19 pandemic, this process was disrupted, and the mental health of the parents was affected.

Research motivation

Although there were many studies on the effects of the COVID-19 pandemic in the literature search, it was observed that there was very limited information on mental health effects on the parents of children with ASD, and there was no systematic review on this topic.

Research objectives

In this systematic review, it is aimed to determine the mental health status of the parents of children with ASD in the COVID-19 pandemic.

Research methods

Articles in English, which could be accessed in full text without any limitation of publication year and country, were included in the study. The systematic review was conducted according to the PICOS strategy (Participants: The parents of children with ASD; Interventions: Effects of COVID-19 pandemic on mental health; Comparators: The parents of children without ASD; Main outcomes: Anxiety, stress, difficulty in coping, loneliness, inadequacy of support systems, social isolation, change in routines and financial difficulties; Additional outcomes: Exercise at home, practicing yoga and meditation, reading newspapers, receiving support from a therapist, cooking meals, talking to their loved ones on online platforms during the pandemic. These results have been reported in studies and included and presented in this systematic review. Study design: Quantitative/qualitative studies). The search results were reached by browsing the Web of Science, PubMed (including MEDLINE), Cochrane, Scopus, Science direct and Google Scholar databases using the keywords COVID-19 AND ("autism" OR "autistic" OR "autism spectrum disorder") AND parent AND ("mental health" OR "anxiety" OR "stress"). The list of the references of the included studies was reviewed to access additional studies.

Research results

The systematic review was conducted according to the PICOS strategy, and a total of 12 studies were included in a quantitative and qualitative design. The studies have revealed that parents are negatively affected by the COVID-19 pandemic. It was reported that the parents of children with ASD had increased anxiety and stress during the pandemic, children became aggressive as their routines changed, and the parents had difficulty coping with this process. During the pandemic, the parents met with their friends *via* online platforms, practiced yoga and meditation, the spouses provided rest breaks to each other and received support from therapists.

Research conclusions

The COVID-19 pandemic negatively affected the mental health of children with ASD and their parents. It may be recommended to plan more interventions that will positively affect the mental health of parents and support them.

Research perspectives

Given the uncertainty of how long the COVID-19 pandemic will last, it is important to conduct a large number of descriptive and interventional studies on the mental health of parents with children who have ASD. In this systematic review, it was revealed that the number of studies on this topic is quite limited. It is thought that this systematic review will form the basis for future studies.

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Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 August 19; 11(8): 403-506



Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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ABOUT COVER

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INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Lin-YuTong Wang*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
August 19, 2021

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INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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ONLINE SUBMISSION
https://www.f6publishing.com

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World Journal of Psychiatry

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World J Psychiatr 2021 August 19; 11(8): 403-411

DOI: 10.5498/wjp.v11.i8.403

ISSN 2220-3206 (online)

THERAPEUTIC AND DIAGNOSTIC GUIDELINES

Ultra-brief crisis interpersonal psychotherapy based intervention for suicidal children and adolescents

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Author contributions: Klomek AB wrote the protocol and this article that describes it; Catalan LH contributed equally to this work; she wrote the protocol and the article as well; Apter A conceived the initial idea and was involved in writing the protocol and the article; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Abstract

Suicidal behaviors in adolescence are a major public health concern. The dramatic rise in self-injurious behaviors among adolescents has led to an overwhelming increase in the number of those presenting to the emergency rooms. The intervention described below was constructed on the basis of brief and focused interventions that were found to be effective among suicidal adults using an adaptation of interpersonal psychotherapy for adolescents. The intervention has four main objectives: first, a focused treatment for reducing suicide risk; second, a short and immediate response; third, building a treatment plan based on understanding the emotional distress and interpersonal aspects underlying suicidal behavior; and lastly, to generate hope among adolescents and their parents. The intervention includes intensive five weekly sessions, followed by 3 mo of email follow-up.

Key Words: Suicide; Depression; Adolescents; Crisis intervention; Interpersonal psychotherapy

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Core Tip: Waiting time for treatment for adolescents who are at risk for suicide in Israel is unreasonably long. The purpose of the interpersonal psychotherapy based intervention for suicidal children and adolescents is to allow more children to receive an acute preventive intervention within a reasonable period of time. The initial phase

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Manuscript source: Unsolicited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Israel

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 10, 2021
Peer-review started: May 10, 2021
First decision: June 23, 2021
Revised: July 6, 2021
Accepted: July 15, 2021
Article in press: July 15, 2021
Published online: August 19, 2021

P-Reviewer: Kotzalidis GD
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Guo X

includes building a safety plan, understanding the emotional and interpersonal aspects underlying the suicide risk and formulating a problem area. The middle sessions include learning and practicing emotional, behavioral and interpersonal skills. The termination session includes building a treatment plan for relapse prevention and providing hope.

Citation: Klomek AB, Catalan LH, Apter A. Ultra-brief crisis interpersonal psychotherapy based intervention for suicidal children and adolescents. *World J Psychiatr* 2021; 11(8): 403-411
URL: https://www.wjgnet.com/2220-3206/full/v11/i8/403.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i8.403

INTRODUCTION

Suicidal behaviors in adolescence are a major public health concern; recent elevation in adolescents suicidality highlight an increasing need for its prevention and treatment. The prevalence of non-fatal suicidal acts among children and adolescents is considerably high. In fact, suicide risk is the most frequent reason for presentation to psychiatric emergency rooms among this population[1]. Risk factors for suicide are numerous and utterly complex. Particularly, non-fatal self-injurious behaviors, which are generally recurring, constitute an especially elevated risk for suicide[2]. Unrecognized and/or untreated depression is the psychiatric disorder that is the most commonly associated with suicide[3]. Inappropriate management of depression may produce a range of adverse outcomes for children and adolescents, such as school failure and dropout, avoidance of friends, eating disorders, substance and alcohol abuse and of course the propensity to self-harm[3].

The dramatic rise in self-injurious behaviors among children and adolescents has led to an overwhelming increase in the number of those presenting to the emergency rooms worldwide[1]. In Israel each year, about 400 such incidents are accepted to our emergency room at Schneider Children's Medical Center, with about a hundred of these cases necessitating subsequent treatment[4]. As a result, the average waiting time for treatment before the current study was about 12-18 mo; such a lengthy delay often culminated in deterioration of the child's condition and led to an increased probability of adverse consequences. Evidently, the need to develop a brief and targeted intervention for this population is unequivocal. The need for emergency intervention has become even more important due to the coronavirus disease 2019 pandemic. Many countries reported an increase in suicide rates among children and adolescents during this period[5]. Studies among suicidal adults have demonstrated the efficacy of brief and focused treatments in reducing suicide risk[6]. For example, receiving postcards from a clinic was found to reduce suicidal behaviors over time[7].

Interpersonal psychotherapy for adolescents (IPT-A), a manualized, short-term (12 sessions) therapeutic intervention for adolescents with depression[8] is among the most common forms of therapy provided at our clinic. We decided to attempt to lessen the number of sessions even further in the hope of reducing our waiting list and enable a larger number of adolescents to receive therapeutic care. The rationale for selecting IPT-A specifically is based on present research linking interpersonal problems to suicide risk[9]. Previous studies found that individuals at risk for suicide suffer from significant challenges in their relationships[10]. Insecure attachment, in particular, has been identified as a major risk factor for adolescent suicidality[11]. In addition, difficulty expressing and sharing feelings with others has been found to significantly increase the risk of severe suicide attempts, above and beyond the contribution of depression and hopelessness[12].

IPT BACKGROUND

IPT is a commonly used, evidence-based, time-limited treatment for depression in adults[13] and adolescents (IPT-A)[8,14] as well as other psychiatric disorders (*e.g.*, anxiety disorders)[15]. IPT has demonstrated efficacy in reducing depressive symptoms and improving overall performance and social functioning[16]. IPT-A is an

adaptation of IPT tailored specifically for adolescents with depression[8]. Similar to the original adult version, IPT-A is time-limited and evidence-based[8]. IPT-A focuses on addressing the link between depressed mood and current interpersonal problems. The goal of IPT-A is to reduce depressive symptoms and improve interpersonal functioning by identifying an interpersonal problem area of focus and developing communication/interpersonal, emotional skills and problem-solving strategies[8].

Recently, a number of studies documented the potential for effectiveness of IPT in treating suicidal patients. Mufson *et al*[17] presented preliminary outcomes of a small sample of suicidal adolescents treated with IPT-A (IPT-A-Suicide Prevention). Tang *et al*[18] examined the effects of intensive interpersonal psychotherapy for adolescents with depression who were at risk for suicidal behavior and compared these adolescents with patients who received treatment as usual at schools. Results illus-trated lower post-intervention severity of depression, anxiety, suicidal ideation and hopelessness among those treated with intensive IPT-A compared to treatment as usual.

To the best of our knowledge, despite the tremendous service gap and devastating consequences of the global suicide epidemic among children and adolescents, no protocol exists that offers a very short, practical and feasible crisis intervention for children and adolescents who are at risk of suicide. The intervention described below was constructed on the basis of brief and focused interventions that were found to be effective among suicidal adults using an adaptation of IPT-A.

INTERPERSONAL PSYCHOTHERAPY BASED INTERVENTION FOR SUICIDAL CHILDREN AND ADOLESCENTS

The efficacy of IPT based intervention for suicidal children and adolescents has been recently published elsewhere[4]. The following is a thorough description of the intervention itself. The intervention has four main objectives: first, a focused treatment for reducing suicide risk; second, a short and immediate response to be able to deliver the intervention within a month from the date of referral; third, building a treatment plan based on understanding the emotional distress and interpersonal aspects underlying suicidal behavior and the associated, distinct difficulties of the patient (such as interpersonal skills deficits and emotion dysregulation); and lastly, to generate hope among patients and their parents. Our assumption is that achieving these four goals allows the patient and parents to feel that things can get better, which in turn helps to decrease the patient's suicide risk.

Structure of the intervention

The intervention is comprised of an intensive phase of five weekly sessions and a follow-up phase consisting of four emails across a 3 mo period. The emails are sent to both the adolescent and his/her parents. In the first month post-intervention, two emails are sent (one email every 2 wk). In the following 2 mo, two additional emails are sent (an email every month) for a total of four follow-up emails (Figure 1).

Parental involvement: The intervention is intended for children and adolescents ages 6-18-years-old. We require parental attendance at the first and final sessions and invite parents to attend additional sessions as needed. For children under 10 years of age we recommend that the parents be present during all five sessions.

The intensive phase: The intensive phase is based on IPT-A with the addition of some elements adapted from Cognitive Behavioral Therapy for Suicide Prevention[19] and Dialectical Behavioral Therapy[20].

The first and second sessions constitute the initial phase of the acute intervention and involve assessment and diagnosis of depression and suicide risk (risk assessment), interpersonal assessment and problem area formulation. The third and fourth sessions comprise the middle phase of the acute IPT-A intervention, which focuses on fostering emotional and interpersonal skills within the specific problem area. The termination phase includes the final fifth session in which the patient and therapist summarize the therapeutic process, and the therapist provides recommendations for further treatment. Below is a detailed description of each session.

First session

The first session should ideally include both patient and parents to establish initial rapport and commitment as well as focus on depression and suicidal risk. It is an

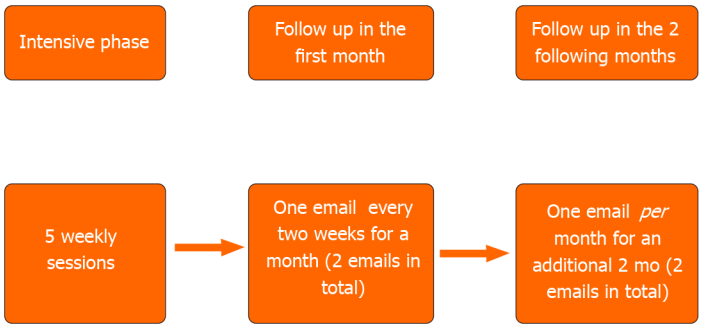


Figure 1 The intervention is comprised of an intensive phase of five weekly sessions and a follow-up phase consisting of four emails across a 3 mo period.

especially intensive meeting requiring an active therapeutic approach and should include:

(1) Risk assessment: A short risk assessment is conducted in addition to the initial risk assessment generally conducted at the intake. This portion of the first session includes an evaluation of depressive symptoms using scales like the Mood and Feelings Questionnaire[21] as well as an assessment of suicidality based on the Columbia Suicide Rating Scale[22] and/or Suicide Ideation Questionnaire[23].

(2) Safety plan[24]: In the event of suicidal risk, an interpersonal safety plan is constructed in collaboration with the patient and the parents. The safety plan includes a list of coping strategies arranged in a hierarchical order, available for the patient, should a suicidal crisis occur. The main purpose of the plan is to provide a predetermined course of action for potential coping strategies as well as a list of specific and relevant support resources. The plan includes internal strategies that a patient employs on his own (*e.g.*, self-talk) in addition to a list of contacts of individuals in the patient's life (*e.g.*, family members, healthcare providers) who can be contacted in real time to help reduce the risk of suicidal behavior. A collaborative approach is recommended between the therapist, the patient and the parents. The plan is a dynamic therapeutic program reviewed periodically by the patient and therapist to evaluate the need for any particular changes or additions.

(3) Chain analysis: A chain analysis is performed in order to outline and discern the events that occurred in the hours prior to the attempt. The chain analysis allows for better understanding of the context of the suicidal act and the emotional and interpersonal/social triggers preceding the attempt.

(4) Presenting the intervention to adolescents and their parents: A thorough explanation of the nature, structure and goals of the intervention is presented to the adolescent and parents. The need for parental cooperation is addressed directly, and the topic of confidentiality is discussed. Further, the obligation to share details of the patient's risk and needs with the school is discussed. The goal of collaboration with the school is to increase the support the patient receives from the school in the areas he struggles the most (*e.g.*, academic, social or emotional realms). Although the communication with the school is addressed in the first session, in practice the school is contacted only after the end of the second session, once we have gotten to know the patient better and have jointly delineated with the patient the main problem area that underlies his/her suicidality. Finally, the limitations of the intervention and the need for long-term psychological treatment and/or consultation about psychotropic medication are addressed. The family is accompanied throughout the intervention in the challenge of finding appropriate follow-up care after the acute IPT-A for suicidal children and adolescents intervention.

and (5) Psychoeducation: Extensive psychoeducation about depression, suicidality, adolescence, parenting and other patient-specific topics is provided. The patient is presented with an explanation of the concept that suicidal crises come in waves and that the purpose of the intervention is to prepare for the next wave. The underlying assumption is that it is likely there will be more crises in the future even if, at the moment, the patient is feeling better. We also use the IPT-A concept of a "Limited Sick Role," which is an aspect of the medical model of IPT. This role refers to the need to match expectations between functional requirements and the patient's mood. The patient is encouraged to function to the best of his ability, while adjusting the pace and progress to his mental state. The concept of the limited sick role is also explained to the patient's parents and teachers.

Second session

Each session begins with an evaluation of the patient's mood and suicidal risk on a scale of 0-10 and discussion about the changes needed in the safety plan. While the first session focuses on the depression and suicidal risk, the second session concentrates on interpersonal functioning. The purpose of the second session is to define the problem area that will be the main focus of the intervention. In order to achieve this, the therapist uses the Closeness Circle and the Interpersonal Inventory[25]. The Closeness Circle is a series of circles, one inside the other (Supplementary material 1). The therapist explains that the circles around the patient's name represents circles of closeness, and the goal is to place the patient's significant relationships within the appropriate circles according to the relevant degree of intimacy; the result is a visual representation of the patient's significant relationships. Then, the therapist and the patient discuss the patient's meaningful relationships using the Interpersonal Inventory. The Interpersonal Inventory includes questions related to facts, opinions, particular events and feelings about the relationships with the people outlined in the patient's circles. The goal of this session is to reach as deep of an understanding as possible of the patient's emotional and interpersonal world and to identify the most relevant emotional and interpersonal struggles that may be the underlying issues contributing to the patient's suicidal risk.

The first two sessions lead to the formulation of the main problem area that the patient is currently dealing with[25]. The problem area is a framework in which the patient and therapist learn and practice skills in the middle phase of the intervention. The line of questioning taken by the therapist in exploration of the various potential problem areas (*e.g.*, grief, conflicts, role transitions and interpersonal deficits) should be directed towards obtaining relevant information in order to ascertain which is currently most significant. There are four main problem areas: (1) grief: relates to actual death and refers to situations in which depression developed due to complicated grieving following the loss of a significant other; (2) interpersonal disputes: conflicts or problems managing expectations in significant relationships. With adolescents this is usually between the patient and his/her parents but may also occur with a teacher, sibling or friend; (3) role transitions: significant life events that may be positive or negative and can be identified as the point at which the patient became depressed such as entry to middle/high school, parental divorce or a diagnosis of an illness; and (4) interpersonal deficits: difficulties with interpersonal skills, leading to loneliness or social detachment. The problem can be in social/group settings or intimate/dyadic situations. It is important to establish an understanding of the specific hardships involved, such as asking for help, learning to forgive, dealing with disagreements in groups, *etc.*

During or after the second session, the therapist contacts and communicates with the school staff.

Sessions three and four

These sessions are focused on fostering and practicing interpersonal, emotional and behavioral skills. Each session begins with an examination of the patient's mood during the past week as well as his suicidal risk. The safety plan is reviewed and readjusted. These two sessions focus on skills learning and practicing within the formulated problem area.

As there is very little time within this brief intervention for skill learning, the therapist should choose one or two IPT-A skills that the patient exhibits the greatest deficits in and that are most relevant to his suicidal risk. These skills are typically related to mood and/or interpersonal relationships. There are three skill sets to choose from including emotional, behavioral and interpersonal. Emotional skills include an emphasis on emotional regulation techniques. The work on emotions with these at-risk children and adolescents include raising their awareness to the various emotions, cultivating their ability to label their emotions, monitoring their intensity and learning ways to regulate them in order to control behaviors associated with these feelings. This promotes the patient's realization and understanding that it is normal to feel lonely, sad or hopeless at times. Yet, when these emotions are intensive and overwhelming, the adolescent should act to control their behavior. Behavioral skills include decision analysis (interpersonal problem-solving), which are crucial in every type of interpersonal interaction. Lastly, enhancement of interpersonal skills incorporates communication analysis, in which the patient learns to identify maladaptive communication skills and learns flexible and adaptive alternatives. All skills are taught through role-play and entail interpersonal experiments intended to be conducted between sessions (*i.e.* in real life) and processed with the therapist during the sessions

themselves. Many of the parents benefit from these skills training as well and are therefore encouraged to attend these sessions as needed.

Session five

The concluding session of the intensive phase includes a summary of the interpersonal and emotional work that has taken place and recommendations for further treatment. In this session we re-emphasize that suicidal risk and behaviors occur in waves and address the possibility that the adolescent may feel suicidal again by discussing relapse prevention. We return to the safety plan devised together in the beginning of treatment in order to ensure its relevance and verify that the patient is familiar with it and willing to use it when needed.

Follow-up phase

Following the intensive phase, periodic emails are sent to the patient and his parents over a 3 mo timespan. During the first month following termination, an email is sent every 2 wk. Then, during the following 2 mo, one email is sent each month. The emails are sent to the patient's personal e-mail and/or his parent's email depending on the patient's age and preferences.

The email is written in a fixed format and is sent directly from the clinic. The email includes patient-specific information in order for it to be personalized (Supplementary material 2).

CASE STUDY

Background

Rona (pseudonym) is a 16-and-a-half-year-old, 11th grade student. She lives with her parents and two brothers in a city in the center of Israel. Her father is a software engineer, and her mother works as a teacher. Both parents were born in the Soviet Union and immigrated to Israel in their early 20s.

Rona presented with a significant suicide attempt in which she swallowed 50 pills with an intention to die. The psychiatric evaluation concluded that she was diagnosed with depression. She began anti-depressant medication and was simultaneously referred for IPT-A for suicidal children and adolescents.

First session

Assessment and psychoeducation: The first session took place with Rona and her parents. After taking Rona's history, psychoeducation was provided, focusing primarily on symptoms of depression and suicide prevention. Further, the intervention itself was explained in terms of its structure, content and goals and the need to find continued, psychological care post-treatment even though we just started.

The next step was performed with Rona alone. A clinical evaluation of depressive symptoms and suicidal risk was repeated, and Rona completed a few self-report questionnaires. In the clinical assessment, Rona denied current suicidality. She stated she understood she had made a mistake attempting suicide and declared she would avoid future attempts. She denied suicidal ideation and intent to die. She also reported significant improvement in her depressive symptoms. Her questionnaires indicated significant depression (Mood and Feelings Questionnaire = 29), moderate severity of suicidal ideation (Suicide Ideation Questionnaire = 33) and high suicide risk (Columbia Suicide Rating Scale = 5).

Safety plan: The next step included a collaborative drafting of a safety plan with Rona. Although Rona insisted it was unnecessary, the need to build a plan for handling potential suicidal waves was explained to her. Rona was cooperative, and the program seemed to be a good fit for her (Supplementary material 3). Despite the proper plan and the fact that Rona denied suicidal risk, we kept in mind the immense gap between the current circumstances and the serious suicide attempt she had made just a month prior to her referral. A substantial portion of the present therapeutic intervention focused precisely on this gap.

Chain analysis: From the chain analysis it became evident that the night before the suicide attempt, Rona was very stressed because of an exam she was supposed to take the next day at school. She knew that she had not studied properly and was extremely afraid that she would fail. She felt that she could not afford to fail this exam especially because she knew how much her failure would disappoint her father.

She tried not to think about it and watched TV, but she could not concentrate. She only imagined the reaction of her father when he finds out that she failed the exam. She was not able to sleep all night. When the day started the pressure increased, and there seemed to be no other solution. She felt stressed and helpless. She got ready for school as if she were planning on going, her parents wished her luck on the exam and left for work. She was left alone at home and finally decided she was not going to go to school. She felt desperate. She went to her shower and saw a packet of pills. She felt that she would rather die than face whatever would happen if she went on with her day as planned. She took all the pills in the container. Her mother found her half an hour later, in the bath with the pills next to her. When Rona recovered in the hospital and saw her parents, she was very disappointed to find that she was still alive and felt awfully guilty and ashamed.

After we conducted the chain analysis, we came back to the safety plan and addressed the need to use it whenever stressful events occur. Towards the end of the session, we invited the parents to rejoin and shared with them the safety plan; we clarified what was required from them when Rona approaches them in times of crisis.

Second session

The second session focused on the interpersonal assessment; to enhance this process we used the Closeness Circles and the Interpersonal Inventory. Rona had many people in the circles (Supplementary material 1), and it seemed she had many significant individuals in her life. She described close and meaningful relationships with her friends, juxtaposed to the fact that she recently moved away from them. Her father was in the closest circle to her. She described a special and close relationship with him that was different from her father's relationship with her brothers. She explained that her academic success was always important to her father and that when she was younger, he tutored her for many hours. However, Rona explained she was not invested in her studies and preferred to spend time with her friends; she described ongoing conflicts between her and her father about it. Rona felt that her dad did not understand her needs. In the last year she was less invested in her studies, and this negatively impacted her relationship with her father. Rona felt he was dissatisfied with her and believed he was distancing himself from her. She felt that the two were no longer as close as they used to be. Rona shared that she missed the closeness they had, and she felt she failed to be the daughter her father wanted her to be. Further, Rona shared her parents' relationship was deteriorating and that they quarreled often. In the past, Rona's father had shared with her some of his feelings about her mother, and Rona felt that she understood her father better than her mother did. She missed being the one her father trusted and confided with.

Rona's mother was in the second circle. Rona describes she was never very close to her mother and felt that her mother was unable to truly understand her. Rona described she did her best to help around the house whenever her mother asked her to, which she felt helped avoid arguments with her mother and assisted in maintaining a somewhat normal relationship between the two of them. There was no real closeness between Rona and her mother, but Rona insisted it did not bother her and that their relationship was this way as long as she could remember. The more we talked about their relationship, the more likely it seemed that Rona actually wished to be closer to her mother but that she was too afraid to expect intimacy with her and be disappointed.

In the third circle Rona wrote her ex-boyfriend. Rona shared she decided to break up with him 2 mo ago because she felt she was no longer fun to be around and that she would probably disappoint him soon as she disheartened others in her life. She felt she was changing; she was no longer in the mood to hang out with friends and found she mostly preferred to be alone. After the interpersonal inventory, we introduced Rona to the concept of problem areas and collaboratively chose the problem area of interpersonal disputes (surrounding her conflicting relationship with her father).

Session three and four

Learning skills: The third and fourth sessions focused on skill acquisition and rehearsal. The goal was to teach Rona skills that would help her communicate better with her father (communication skills) as well as skills that would help her respond differently if she felt similarly to how she felt prior to her suicide attempt (emotional regulation skills). We used communication analysis and identified the need to work on Rona's ability to speak more openly with her father and express her feelings to him without fearing she would be disappointing him. Through communication analysis we were able to uncover that Rona predominantly avoided discussing her school difficulties with her father or share with him that she wished to be more engaged in

other activities such as spending time with her friends.

Together, we brainstormed some goals Rona wished to achieve in a potential conversation with her father. Rona wanted to relieve stress from her studies and accomplishments without feeling she would be disheartening her father too much. We planned numerous possible scripts for the conversation and used the teen tips to promote effective communication. Between sessions, Rona practiced her communication skills with her father, eventually introducing a possibility for a different kind of dialogue between them.

Further, sessions centered on fostering Rona's emotional regulation skills. At first, Rona found it difficult to recognize the feelings she experienced before attempting suicide (*e.g.*, the fear of disappointing her father, hopelessness and loneliness, in particular). She was only able to describe she felt she was "under pressure." Through processing Rona's feelings prior to the attempt, we were able to elucidate Rona's explicit fear of disappointing her father, which led her to distance herself from him initially and avoid others subsequently, the latter behavior culminating in a detrimental increase in her feelings of loneliness and sadness. Between sessions Rona was requested to monitor the intensity of her negative emotions in various situations, and together we practiced numerous self-calming methods such as self-talk and relaxation techniques. Further, Rona was asked to practice additional soothing techniques at home, and these skills were added to her safety plan. Our intention was to teach Rona to recognize situations in which she would be likely to have a decreased ability to regulate her emotional state, so that once becoming aware of them she would have adaptive means of calming herself.

Fifth meeting

As described above, the objectives of the fifth session are to summarize the therapeutic process, focus on relapse prevention, provide recommendations for further treatment and review the safety plan. The meeting was divided into two parts; in the first half of the meeting we met Rona alone, and her parents joined us in the second part of the session. We addressed the focus of Rona's difficulties, her experiences and her needs in the relationships with her parents. Her parents were invited to express their desire for closeness in addition to their concern for her well-being. We repeated and reevaluated the safety plan with Rona and later with the parents to ensure each of them was knowledgeable of what to do should Rona feel suicidal again.

Although the need for continuous treatment for Rona had been discussed earlier in treatment, present difficulties of finding available individual psychotherapy in the community disabled her immediate transition into follow-up care. Rona was waitlisted for long-term treatment at our clinic, and in the meantime, the family began family therapy.

CONCLUSION

At the end of the intervention, there was a significant reduction in Rona's depressive symptoms, and she continued to deny current suicidal ideation. The family remained in family therapy for 8 mo, and treatment was found to be helpful and led to tremendous therapeutic gains. A year later, Rona began long-term treatment at our clinic. Of note, throughout this period, Rona refrained from further engagement in suicidal behaviors.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 August 19; 11(8): 412-428

DOI: 10.5498/wjp.v11.i8.412

ISSN 2220-3206 (online)

REVIEW

Menopause and cognitive impairment: A narrative review of current knowledge

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Author contributions: The authors declare equal contributions to this manuscript.

Supported by National Council for Scientific and Technological Development of Brazil (CNPq), No. 312400/2018-7.

Conflict-of-interest statement: The authors declare no conflicts of interest related to this article.

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Abstract

A severe impairment of cognitive function characterizes dementia. Mild cognitive impairment represents a transition between normal cognition and dementia. The frequency of cognitive changes is higher in women than in men. Based on this fact, hormonal factors likely contribute to cognitive decline. In this sense, cognitive complaints are more common near menopause, a phase marked by a decrease in hormone levels, especially estrogen. Additionally, a tendency toward worsened cognitive performance has been reported in women during menopause. Vasomotor symptoms (hot flashes, sweating, and dizziness), vaginal dryness, irritability and forgetfulness are common and associated with a progressive decrease in ovarian function and a subsequent reduction in the serum estrogen concentration. Hormone therapy (HT), based on estrogen with or without progestogen, is the treatment of choice to relieve menopausal symptoms. The studies conducted to date have reported conflicting results regarding the effects of HT on cognition. This article reviews the main aspects of menopause and cognition, including the neuroprotective role of estrogen and the relationship between menopausal symptoms and cognitive function. We present and discuss the findings of the central observational and interventional studies on HT and cognition.

Key Words: Menopause; Cognition; Dementia; Estrogens; Hot flashes; Cognitive decline

s/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 15, 2021
Peer-review started: February 15, 2021
First decision: June 24, 2021
Revised: July 5, 2021
Accepted: July 28, 2021
Article in press: July 28, 2021
Published online: August 19, 2021

P-Reviewer: Glumac S, Lee KS, Seeman MV
S-Editor: Fan JR
L-Editor: A
P-Editor: Li X

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Core Tip: Cognitive complaints are more common in postmenopausal women than in premenopausal women. Due to the reduction in ovarian function, a progressive decrease in serum estrogen levels occurs, leading to menopausal symptoms with an emphasis on vasomotor symptoms. In addition to these symptoms, cognitive impairment can affect postmenopausal women to varying degrees. Several aspects of the relationship between menopause and cognitive function were reviewed. We report the latest evidence on the topic. In this sense, considering current knowledge, we do not recommend the prescription of hormone therapy to prevent cognitive decline or dementia in postmenopausal women.

Citation: Conde DM, Verdade RC, Valadares ALR, Mella LFB, Pedro AO, Costa-Paiva L. Menopause and cognitive impairment: A narrative review of current knowledge. *World J Psychiatr* 2021; 11(8): 412-428
URL: https://www.wjgnet.com/2220-3206/full/v11/i8/412.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i8.412

INTRODUCTION

Approximately 50 million people worldwide live with dementia, with Alzheimer's disease (AD) being the most frequent cause[1]. Dementia is characterized by severe cognitive decline and subsequent functional disability[2]. It is the fifth leading cause of death and is responsible for 28.8 disability-adjusted life-years[3]. A few decades before the onset of Alzheimer's dementia, AD-related neuropathological changes are observed in the brain, which may be accompanied by subtle cognitive decline[4]. Accordingly, patients with early cognitive symptoms are at increased risk of dementia [5,6].

Mild cognitive impairment (MCI) is defined as individuals with objective cognitive deficits in neuropsychological tests (usually defined as a performance of 1.5 standard deviations below the mean established for age and education) and preserved functional independence for activities of daily life[2]. MCI is related to a nine-fold increase in the risk of dementia compared to the general population[5]. Subjective cognitive complaints with normal performance on neuropsychological tests are related to a two-fold increase in the risk of dementia compared to the general population[6]. Identifying and understanding the predisposing and triggering factors of the neurobiological mechanisms underlying early cognitive decline may contribute to the development of preventive interventions to mitigate the risk of dementia.

Female sex is a consistent risk factor for dementia, and the greater longevity of women does not fully explain this relation. In addition, estrogen plays an essential role in the neurobiology of cognitive processing and neuronal function, and the menopausal transition is associated with subtle cognitive decline. However, the relationships among decreased estrogen levels in menopause, the effects of hormone therapy (HT) on cognition, and the risk of dementia are still conflicting and puzzling.

Considering the relevance of the issue and seeking to contribute to the existing literature, several aspects of the relationship between menopause and cognitive function were reviewed in this paper. We describe the most recent evidence, presenting what we know and the gaps in knowledge on the subject.

SEARCH METHODS

A search was conducted in Medline and Embase for the period from 1980 to 2020. The search terms cognition, climacteric, cognitive decline, estrogen effects, menopause, menopausal symptoms, hot flashes, middle-aged women, perimenopause, neuropsychology, HT, progestogen, MCI, subjective cognitive decline, risk of dementia, neuroimaging, and vasomotor symptoms were used.

Original articles, systematic reviews, meta-analyses, narrative reviews, and consensus reports were evaluated. Both human and animal studies published in

English were considered. The bibliographies of the articles were searched to identify related studies. All articles were critically evaluated by the authors, including those more specifically related to the theme of this narrative review and those that resulted in agreement between the authors for their inclusion.

EVIDENCE OF THE RELATIONSHIP BETWEEN MENOPAUSE AND COGNITIVE DECLINE

Subjective cognitive decline is one of the most frequent complaints of women undergoing the menopausal transition, with a 44%-62% prevalence estimated in population-based studies[7,8]. Reports of memory problems are associated with the perimenopausal period compared to pre- or postmenopausal periods[9]. The incidence of MCI was 4.5% in 6376 postmenopausal women evaluated for 5.4 years in the Women's Health Initiative Memory Study (WHIMS)[10], but the relationship between MCI and menopausal factors has still been poorly studied. In contrast, changes in women's cognitive test performance, regardless of cognitive complaints or cognitive impairment, are consistently related to the reproductive period and menopausal transition.

After adjusting for age, cognitive performance during postmenopause tended to be lower than that during pre- and perimenopausal periods, particularly verbal delayed memory and executive function[11], which involve cognitive domains that are assumed to be more sensitive to changing estrogen levels[12]. The Study of Women's Health Across the Nation evaluated 2362 American women by repeated administration of neuropsychological tests for four years. Women's scores on delayed and immediate memory tests in the early and late perimenopausal periods did not improve over time with test repetition. However, the incremental changes in scores normalized in the postmenopausal period, returning to the pattern observed during premenopause[13]. Similarly, Kilpi *et al*[14] studied 2411 middle-aged United Kingdom women, verifying that processing speed and immediate and delayed verbal episodic memory decreased in the perimenopausal period; additionally, changes in verbal episodic memory tests correlated with follicle-stimulating hormone and luteinizing hormone levels.

Several studies have also reported that prolonged lifetime estrogen exposure results in better cognitive outcomes[15]. A younger age at first menses, older age at menopause, age at birth of a first child more than 20 years, and an extended reproductive period were related to a more remarkable performance on neuropsychological tests at postmenopause[16,17]. However, the data are conflicting regarding reproductive period factors and the risk of progressive cognitive decline or dementia. Although the meta-analysis by Georgakis *et al*[15] found that age at menopause and the reproductive period were not associated with the risk of dementia, two more recent population-based studies documented an increased risk of dementia by up to 23% with late menarche, early menopause and a short reproductive period[18,19]. Interestingly, patients who underwent bilateral oophorectomy before menopause had a higher risk of cognitive impairment over time than age-matched natural menopausal women; additionally, oophorectomy at ≤ 45 years of age was associated with an increased risk of dementia[20,21]. In women with Down syndrome, a condition with a higher incidence of AD than the general population, age at menopause was directly correlated with the age of dementia onset[22].

Evidence on AD biomarkers in middle-aged women strengthened the hypothesis that decreased estrogen levels in the menopausal transition explain cognitive decline during perimenopause and the greater risk of dementia related to the female sex. Rahman *et al*[23] compared 40- to 65-year-old women with age-matched men in terms of cerebral volumetry using structural magnetic resonance imaging, cerebral metabolism using 18F-fluorodeoxyglucose positron emission tomography, and the β-amyloid load using 11C-Pittsburgh compound B positron emission tomography. Women presented lower gray and white matter volumes, lower glucose metabolism, and higher deposition of β-amyloid; this neuroimaging pattern was consistent with an AD endophenotype. Menopause was the strongest predictor of these findings. Other studies reported a gradient of AD biomarkers, with the most remarkable abnormalities in menopausal women, an intermediate number of abnormalities in perimenopausal women, and the lowest number of abnormalities in premenopausal women[24,25]. In addition, cerebral glucose hypometabolism in AD-vulnerable regions of peri- and postmenopausal women correlated with reduced platelet mitochondrial cytochrome oxidase activity; mitochondrial cytochrome oxidase is an enzyme involved in

adenosine triphosphate (ATP) synthesis that is regulated by estrogen[24]. Based on these findings, the decrease in estrogen levels during the menopausal transition disrupts brain bioenergetics due to mitochondrial cytochrome oxidase dysfunction that is accompanied by reduced cerebral metabolism, β-amyloid deposition, synaptic loss, and cognitive decline.

PATHOPHYSIOLOGY

Estrogen and the brain

Accumulating evidence shows a significant neurotrophic and neuroprotective effect of estrogen on the central nervous system. Cognitive deficits have been described in women during the menopausal transition, particularly in cognitive domains such as working memory, attention, reduced processing speed, and reduced verbal memory. This review briefly describes the plausible biological functions of estrogens in aspects of cognitive function and the mechanisms involved[26].

The effects of estrogen on the brain include complex cellular mechanisms ranging from classical nuclear to nonclassical membrane-mediated actions. In classical mechanisms, estrogen modulates gene transcription by interacting with nuclear receptors. The estrogen receptors (ER) α and ERβ have distinct differences in their binding affinities for different ligands and selective ER modulators[27].

Through genomic mechanisms, steroids exert long-term effects on neurons, modulating the synthesis, release, and metabolism of many neuropeptides and neuroactive transmitters and the expression of their receptors. The nongenomic (nonclassical) estrogen action is probably mediated by receptors integrated or associated with the cell membrane and by the activation of distinct intracellular signaling cascades through the high-affinity membrane-associated G protein-coupled estrogen receptor GPR30/GPER1[28,29].

These effects of estrogens include rapid actions on the excitability of neuronal and pituitary cells, activation of cyclic adenosine monophosphate and mitogen-activated protein kinase pathways that affect the activity of targets such as kainite and insulin-like growth factor-1 receptors, modulation of G-protein coupling, modulation of calcium currents, modulation of calcium channels and calcium ion entry and protection of neurons from damage by excitotoxins and free radicals[30-33].

Decreases in estradiol levels may impact three systems. Researchers must determine how therapeutic modulation of estradiol levels may augment normal or disease-related cognitive decline. The three predominant systems postulated to be involved in cognitive aging concerning hypoestrogenism include the basal forebrain cholinergic system, the dopaminergic system, and the mitochondrial bioenergetic system[34].

Reduced nicotinic cholinergic binding sites in the cortex and reduced cholinergic acetyltransferase activity (a marker of cholinergic neurons) have been shown to correlate with reduced cognitive performance[35]. Choline acetyltransferase-expressing neurons are a marker for cholinergic neurons, and thus the expression of GPR30/GPER1 on cholinergic neurons provides increasing evidence for an interaction between estrogens and the cholinergic system. Clinical magnetic resonance imaging studies have shown that estradiol treatment also modulates anti-muscarinic and anti-nicotinic induced brain activity. Estradiol treatment alters anticholinergic-related brain activation during working memory in postmenopausal women[36].

The effects of estradiol on dopaminergic signaling have been less well characterized than its effects on the cholinergic system. *In vitro*, estradiol protects against 6-hydroxydopamine toxicity in dopamine neurons[37]. Magnetic resonance imaging evidence has shown that dopaminergic agonists increase working memory activity, suggesting that the dopaminergic system is responsive to pharmacological manipulation after the menopausal transition[38]. The potential mechanism by which estradiol exerts its neuroprotective effects on dopaminergic neurons is to modulate the neurotoxic effects of the renin-angiotensin system[39].

The mitochondrial aging hypothesis is related to increased mitochondrial DNA damage, leading to increased reactive oxygen species-mediated damage and a reduction in mitochondrial activity[40]. Clinical studies support the postulated role for estradiol in maintaining appropriate mitochondrial bioenergetics; clinical studies also support the hypothesis that decreasing estradiol levels are correlated with reduced synaptic plasticity, an indicator of cognitive performance, suggesting that a failure of glucose metabolism might influence cognitive deficits. As glucose uptake decreases, ATP production also decreases, consistent with aerobic cellular respiration[41].

Finally, low-grade inflammation has also been identified as a potential cause of cognitive decline. Postmenopausal women present an increase in the levels of inflammatory markers such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha. These increases in inflammatory markers appear to be normalized following treatment with sex HT, exerting a relevant anti-inflammatory effect[42,43].

Neuroprotective effect of estrogen

A reasonable hypothesis is that estrogen might exert an important protective effect on the deterioration of cognitive functions that occurs with normal aging. The potential mechanisms involved in the neuroprotective effects of estrogens include modulation of neuropeptides, neurotransmitters, and neurosteroid synthesis and activity[44,45]; reduced cell apoptosis[46]; modulation of neuronal growth and synaptic plasticity[47] and mitochondrial activity[48]; antioxidant properties[49]; modulation of the brain immune system[50]; and reduced formation of β-amyloid[51].

Importantly, the effects of treatment with sex hormones on cognitive symptoms appear to be more evident during the menopausal transition or in the first years of menopause when the levels of estradiol and estrogen receptors are initially decreasing [52].

Moreover, some selective estrogen receptor modulators, such as tamoxifen and raloxifene, have shown promising effects by interacting with ERα, ERβ, and GPR30[53] and exert neuroprotective effects[54]. Selective estrogen receptor modulators have shown efficacy in reducing anticholinergic effects on cognitive performance in some cognitive domains by reducing proinflammatory cytokine levels[55].

Findings from primary studies have shown that testosterone also exerts neuroprotective and anti-inflammatory effects on the brain. Testosterone protects against oxidative stress, serum deprivation-induced apoptosis, and soluble amyloid β (Aβ) toxicity; this effect is mediated by estrogen. Aβ toxicity induced by testosterone appears to involve an androgen receptor-dependent mechanism that leads to the upregulation of the Aβ-catabolizing enzyme neprilysin[56,57].

Notably, testosterone studies in women have yielded differing findings according to the women's ages, the testosterone dose administered, and the study duration. Observational and interventional studies have shown an association between verbal learning and memory and physiological concentrations of testosterone administered to postmenopausal women exogenously. The effects of testosterone on verbal learning and memory in postmenopausal women do not seem to rely on the aromatization of estradiol. The statistically significant improvements in verbal memory following testosterone therapy in postmenopausal women suggest that further investigations of the ability of testosterone to enhance cognitive performance or delay cognitive decline are warranted, but the results currently do not justify using testosterone for this purpose[58].

In conclusion, increasing evidence linking menopausal hormone changes and cognition has revealed a complex biological mechanism. A better understanding of this mechanism is fundamental to enable earlier and personalized pharmacological treatment with the potential to delay the onset of cognitive decline during the menopausal transition.

CLIMACTERIC FACTORS AND COGNITIVE DECLINE

The climacteric period often involves problematic symptoms, including vasomotor symptoms, vaginal dryness, decreased libido, insomnia, and fatigue[59]. In clinical practice, cognitive changes are also frequently observed during this period, with subjective reports of "cerebral fog" affecting daily cognitive performance. Some of the most common symptoms are deficits in attention, processing speed, and memory, which subsequently manifest as lack of focus, slow thinking, and forgetfulness[60].

In the Study of Women's Health Across the Nation with 16065 women between the ages of 40 and 55, 31% of premenopausal women reported complaints of forgetfulness, compared to 44% of women in early perimenopause, 41% of women in late perimenopause, and 41% of postmenopausal women[61]. This study later reported a compromise in cognitive performance, mainly in learning skills during the menopausal transition, with a subsequent improvement in the postmenopausal period. Cognitive changes that occur late after menopause are associated with aging and not with the last menstrual period[8].

In the Kinman women's health investigation, a longitudinal study, the cognitive performance of 694 premenopausal Chinese women was evaluated. Verbal memory,

mental flexibility, verbal fluency, and processing speed were measured at baseline and after 18 mo. An improvement in cognitive test scores was observed, which was expected due to the learning effect of repetition of neuropsychological tests. However, perimenopausal women recorded worse results than those who remained in the premenopause group[62].

Studies indicate that this decreased cognitive performance during perimenopause appears to normalize in postmenopause[8,62]. If this pattern of change in memory during the menopausal transition is valid, the decreases in estradiol levels alone are not likely solely responsible for cognitive changes, as memory appears to recover while decreases in estradiol levels persist[13,63].

Although self-reported vasomotor symptoms (VMSs) are generally not related to memory performance[64], when this relationship was observed using 24-h monitoring to measure physiological VMSs, verbal memory differences were found. Among middle-aged women, moderate to severe VMSs related to worse verbal memory were recorded with ambulatory skin conductance monitors and not self-reported VMSs[65,66].

Another cross-sectional study was performed with women with moderate to severe VMSs. Researchers recorded physiological VMSs using ambulatory monitors associated with or without a diary to record subjective VMSs and performed a battery of neuropsychological tests. A higher frequency of physiological VMSs, but not subjective VMSs, particularly during sleep, was associated with poor verbal memory testing performance[67]. Recently, a study evaluating the association between VMSs and worse memory was replicated in breast cancer survivors, confirming evident associations only with physiological VMSs[68].

Thus, in addition to being passive predictors of depressed mood, sleep problems, and worse quality of life during menopausal transition, VMSs also appear to be linked to the leading indices of physical and neurocognitive health[65,68].

HT AND COGNITION

Although many questions remain about the effects of HT on cognitive function, two factors seem to be consistently involved: Age and time of exposure concerning menopause. Researchers have postulated that a critical window exists that explains the more evident effects of HT when administered early when symptoms manifest and when administered to young women. However, published studies have reported conflicting results in this regard and are presented and discussed below.

Contradictory evidence presented to date

Although a considerable number of studies have examined the effects of HT on cognitive function in postmenopausal women, the results are still conflicting. Some studies showed benefits[69-71], others showed a lack of effect[72-74], and worsening of cognitive function was observed in some, including a more significant risk of MCI and various types of dementia[75,76]. Importantly, observational studies are prone to biases, such as selection bias, type, time of HT use, and age at HT initiation, which are often not controlled. These biases may at least partially explain the divergence between the findings of observational and interventional studies.

Many investigators presented their results for different aspects of HT and cognition at the same time. Because the same study published data on global cognitive function, MCI, and dementia, we chose to discuss the best evidence available, presenting the data jointly, as in the original articles of the critical observational and interventional studies on this topic.

Observational studies

Evidence from older women: The Cache County Study (CCS), a longitudinal, population-based study, investigated the association between HT and global cognitive function. The modified Mini-Mental State Examination (MMSE) was administered to 2073 women over 65 years old with no prior diagnosis of dementia. After three years of follow-up, HT was associated with an apparent benefit in global cognitive function and reduced cognitive decline, especially in older women (75 years or older) and even more so in women older than 85 years[77]. In another CCS publication, the relation between HT and AD was evaluated in 1889 women with an average age of 74.5 years. Compared to nonusers, women who received HT for more than ten years presented a 2.5-fold lower risk of AD incidence[78]. With seven more years of follow-up, the CCS cohort verified that starting HT (any type) within five years of menopause was

associated with a 30% reduction in the risk of developing AD. However, if HT was initiated after five years of menopause, no associations were observed.

Furthermore, if HT was initiated within five years of menopause and used for ten years or more, the reduction observed in AD risk was 37%. Additionally, the use of estrogen alone within five years of menopause reduced the risk of AD by 35%[79], which supports the critical window hypothesis. The main information obtained from the observational studies is shown in Table 1.

In a recent 12-year update of the follow-up of the CCS cohort, which included 2,114 women, a longer HT duration was associated with better cognitive function. Additionally, women who initiated HT within five years of menopause presented better cognitive performance than those who initiated it six or more years after menopause, once again supporting the critical window hypothesis. However, another interesting finding in the CCS was that even women who initiated HT after six years of menopause still presented cognitive benefits compared to women who never used HT [71].

In a French longitudinal study, the Three-City Study, 3310 postmenopausal women aged 65 years and over were followed every two years and were subjected to a series of cognitive tests to examine the association of HT with dementia and some specific cognitive domains. After a 4-year follow-up period, no associations were observed between HT and dementia or AD. Additionally, active HT users had significantly better performance on verbal fluency, working memory, and psychomotor speed tasks than those who never used HT. These associations varied according to the type and duration of HT. The findings of this study suggest that transdermal estrogen combined with progestogen and a lengthier HT duration are better at improving cognitive function. Notably, current HT users exhibited a reduction in the detrimental effect of apolipoprotein E (ApoE) E4, a known risk factor for dementia, on the incidence of dementia and AD. Moreover, starting HT near menopause had no relation to improved cognition[69], potentially refuting the critical window hypothesis.

In another longitudinal study with 5504 postmenopausal women conducted at the Kaiser Permanente Medical Care Program of Northern California, women who used HT only during their midlife period presented a 26% reduced risk of dementia than women who never used HT. Those who used HT in late life experienced detrimental effects, with a 48% higher risk of dementia in the 8-year follow-up[80]. These findings support the critical window hypothesis.

The largest longitudinal study was the Nurses' Health Study, a prospective cohort study that included a subgroup of 13087 participants aged 70 or older to evaluate global cognitive function, attention, verbal memory, and category fluency. Generally, few differences were observed between average cognitive decline when comparing current users or former users of HT and those who had never used it. On the other hand, the data suggest an increased risk of cognitive decline in long-term users (*i.e.*, 5 to 10 years) of estrogen alone or estrogen combined with progestogen, with a greater risk identified in women who initiated HT at an older age than in those who never received HT [relative risk: 1.74; 95% confidence interval (CI): 1.08-2.81]. The authors also did not identify a relation between HT and the ApoE E4 allele. The authors concluded that postmenopausal HT provides no relevant cognitive benefit in older women[76].

In a population-based nested case-control study that included 59 women with AD and 221 controls, no relationship was observed between the use of HT (estrogen with or without progestogen) and AD risk[72], corroborating the findings from a previous case-control study[81]. The Multi-Institutional Research in Alzheimer's Genetic Epidemiology case-control study included 971 postmenopausal women from different countries (426 patients with AD and 545 nondemented patients). HT was associated with a 30% reduction in the AD risk. The ApoE genotype did not influence the relationship between HT and AD. The protective effect of HT was modified by age, as it was observed only in younger women aged between 50 and 63 years, who presented a 65% reduction in the AD risk[82].

These findings suggest that HT use during the first years after the last menstrual period, named the critical window, may protect cognitive function. In another case-control study conducted in Finland, 84739 women diagnosed with AD and 84739 women without an AD diagnosis were included. Systemic HT was associated with a 9% to 17% increased risk of AD, with no significant difference between those who used estrogen alone and those who used estrogen and progestogen in combination. The exclusive use of vaginal estradiol did not increase the risk of AD. Moreover, the age at which HT was initiated (younger than 60 years or older than 60 years) had no effect on the AD risk. Notably, in women who initiated HT before 60 years of age, the increase in the AD risk was associated with the use of HT for ten years or more. The

Table 1 Observational studies on hormone therapy and cognition in women

Ref.	Study	Country	Design	*n* (%)	Age (yr)	Hormone therapy	Main findings
Carlson *et al* [77], 2001	Cache County Study	United States	Longitudinal	2073	≥ 65	ET or EPT	HT reduced cognitive decline
Seshadri *et al* [72], 2001		United Kingdom	Case-control	AD: 59. Controls: 221	Mean: 66.7	ET or EPT	HT was not associated with AD
Kang *et al*[76], 2004	Nurses' Health Study	United States	Longitudinal	13807	≥ 70	ET or EPT	HT was not associated with relevant cognitive benefits
Henderson *et al* [82], 2005	Mirage Study	United States, Canada, Germany	Case-control	AD: 426. Controls: 545	Mean: 71.1	ET or EPT	HT reduced the AD risk by 30%
Ryan *et al*[69], 2009	Three City Study	France	Longitudinal	3130	≥ 65	ET or EPT	HT was not associated with dementia or AD, but current users had better cognitive performance in specific domains
Shao *et al*[79], 2012	Cache County Study extended	United States	Longitudinal	1768	≥ 65	ET or EPT	HT initiated within five years of menopause decreased the AD risk by 30%
Whitmer *et al* [80], 2011	Kaiser Permanente Medical Care Program of Northern California	United States	Longitudinal	5504	Mean in midlife: 48.7	ET or EPT	The use of HT only in midlife reduced the dementia risk. On the other hand, the use of HT in late-life increased this risk
Imtiaz *et al*[70], 2017	Kuopio Osteoporosis Risk Factor and Prevention study	Finland	Longitudinal	8195	46 a 56	ET or EPT	Long-term HT users (> 10 yr) exhibited a 47% reduction in the AD risk
Savolainen-Peltonen *et al* [83], 2019		Finland	Case-control	AD: 84739. Controls: 84739	Mean age at onset of systemic HT: 52	ET or EPT	HT increased the AD risk by 9%-17%, regardless of the age of onset of use and the type of HT

ET: Estrogen-only therapy; EPT: Estrogen-progestogen therapy; HT: Hormone therapy; AD: Alzheimer's disease.

authors concluded that prolonged use of systemic HT might be accompanied by an increased risk of AD, which is not related to the type of progestogen or the age of HT initiation[83].

Few observational studies have evaluated the effects of HT exclusively in younger women. A recent prospective study conducted in Finland with 8195 women between 47 and 56 years of age with a 20-year follow-up showed little evidence of the protective effect of HT on dementia or AD, as only women who reported long-term (*i.e.*, more than ten years) use of HT presented a significant reduction in the AD risk of 47% compared to nonusers[70].

Interventional studies and the critical window hypothesis

As previously stated, the critical window hypothesis postulates that the effects of HT vary according to the moment of exposure, as related to menopause. According to this theory, estrogen administered closer to menopause would exert neuroprotective effects, whereas no benefit or harm would be observed when HT was administered years later[80]. Similarly, an ideal moment would exist to start HT and obtain cognitive benefits. Table 2 shows the main findings from the pertinent randomized clinical trials.

Evidence from older women

Due to possible biases regarding HT in observational studies, clinical trials were conducted to clarify these doubts. The WHIMS is an ancillary study of the Women's Health Initiative (WHI). The WHIMS included women aged 65 years or older. The effect of HT on the incidence of MCI and all-cause dementia (Alzheimer's, vascular and other types) was evaluated in hysterectomized women treated with conjugated equine estrogen (CEE), nonhysterectomized women treated with CEE plus medroxyprogesterone acetate (MPA), and the placebo group.

Table 2 Randomized clinical trials on hormone therapy and cognition in women

Ref.	Study	Country	*n* (%)	Age (yr)	Hormone therapy	Main findings
Shumaker *et al*[75], 2003	Women's Health Initiative Memory Study-WHIMS	United States	HT users: 2229. Placebo: 2303	≥ 65	CEE + MPA	HT increased the dementia risk
Shumaker *et al*[84], 2004	Women's Health Initiative Memory Study-WHIMS	United States	HT users: 1464. Placebo: 1483	65 to 79	CEE alone	Estrogen alone did not decrease the incidence of mild cognitive impairment or dementia
Greenspan *et al*[85], 2005		United States	HT users: 187. Placebo: 186	≥ 65	CEE with or without MPA	HT did not affect cognitive function
Yaffe *et al* [86], 2006		United States	HT users: 208. Placebo: 209	60 to 80	Ultra–low dose unopposed transdermal estradiol	Transdermal estradiol did not affect cognitive function
Espeland *et al*[87], 2010	Women's Health Initiative Study of Cognitive Aging-WHISCA	United States	HT users: 1125. Placebo: 1179	65 to 80	CEE with or without MPA	HT was associated with worsening global cognitive function and some specific cognitive domains. This worsening persisted after the interruption of HT
Espeland *et al*[73], 2013	Women's Health Initiative Memory Study of Younger Women-WHIMSY	United States	HT users: 696. Placebo: 630	50 to 55	CEE with or without MPA	HT did not alter global cognitive function or specific cognitive domains
Gleason *et al* [74], 2015	Cognitive and Affective Study-KEEPS-Cog	United States	HT users: 431. Placebo: 262	Mean: 52.6	CEE + micronized progesterone ortransdermal estradiol + micronized progesterone	HT did not affect cognition
Henderson *et al*[92], 2016	Early *vs* Late Intervention Trial with Estradiol Cognitive endpoints-ELITE-Cog	United States	HT users: 284. Placebo: 283	Early postmenopause: 55.6. Late postmenopause: 64.9	Estradiol with or without micronized progesterone	HT did not affect verbal memory, executive function and global cognition, regardless of whether it was started < 6 yr or ≥ 10 yr after menopause
Espeland *et al*[91], 2017	WHIMSY extended + Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO	United States	WHIMSY-HT users: 701. Placebo: 635. WHIMS-ECHO-HT users: 1402. Placebo: 1478	Two groups: 50 to 54; 65 to 79	CEE with or without MPA	HT prescribed to younger women had no significant effect on cognitive function in the long term. HT administered to older women produced decreased global cognitive function, executive function, and working memory

CEE: Conjugated equine estrogen; MPA: Medroxyprogesterone acetate; HT: Hormone therapy.

In the CCE/MPA arm of the study, in which 4532 women participated (CEE/MPA group: 2.229; placebo group: 2.303), the hazard ratio (HR) for dementia was 2.05 (95%CI: 1.21-3.48; 45 *vs* 22 *per* 10000 person-years; $P = 0.01$), resulting in 23 additional cases of dementia *per* 10000 women *per* year. AD was the most common dementia type in both groups. The effects of treatment on the risk of MCI did not differ between groups (HR: 1.07; 95%CI: 0.74-1.55; 63 *vs* 59 cases *per* 10000 person-years; $P = 0.72$). The authors concluded that HT with the combination of estrogen and progestogen increased the risk of probable dementia in postmenopausal women aged 65 years older. These data indicate a lack of protection from MCI in these women receiving HT [75].

In the WHIMS arm with CEE alone, 2947 participants were included (CEE group: 1464; placebo group: 1483), with ages ranging from 65 to 79 years. No significant differences in the dementia risk (HR: 1.49; 95%CI: 0.83-2.66) and MCI risk (HR: 1.34; 95%CI: 0.95-1.89) were observed between groups. However, the joint analysis of the MCI or dementia risk showed a greater risk for women who received CEE alone than the placebo group (HR: 1.38; 95%CI: 1.01-1.89; $P = 0.04$)[84]. Isolated estrogen therapy did not reduce the incidence of MCI or dementia. Based on the combination of WHIMS data, HT with estrogen alone and CEE/MPA resulted in an increased risk of dementia or MCI in women aged 65 or older, and HT was not recommended to prevent cognitive decline[84].

In two randomized clinical trials with a smaller population of older postmenopausal women, including a study with 373 women and a 3-year follow-up period[85] and another with 417 women and a 2-year follow-up period[86], HT had no significant effect on cognitive function. The WH Study of Cognitive Aging, another ancillary study of the WHI, had two arms, CEE alone and CEE/MPA with matching placebos, and included 2304 women. HT initiated after 65 years of age was associated with worsening global cognitive function and changes in a few cognitive domains; notably, this reduction persisted after the interruption of HT. The authors highlighted that this difference in cognitive function was small and might have no clinical meaning[87].

A meta-analysis that included 16 clinical trials with 10114 women reported no beneficial effect of HT (estrogen with or without progestogen) administered in the short or long term (up to five years) on the cognitive function of older postmenopausal women. Moreover, the authors were unable to establish definitive conclusions on the effects of different administration routes and HT dosages on women's cognitive function[88]. Another meta-analysis concluded that HT is not indicated to prevent cognitive decline or dementia in postmenopausal women[89].

Evidence from younger women

Since younger women more frequently receive HT, its effects on cognitive function when used precociously must be clarified. Clinical trials on this topic are rare.

A systematic review included data from nine randomized, double-blind, placebo-controlled clinical trials of HT with estrogen alone and two with estrogen combined with progestogen, in which cognitive tests were administered to women aged less than 65 years, although the sample size was small. Seven of nine studies reported a small advantage for estrogen treatment in at least one cognitive test, particularly in verbal memory and attention. Only two studies assessed the effect of combined HT (estradiol valerate and dienogest), showing some benefit only on verbal memory[90]. Thus, although scarce, evidence from HT in younger women suggests potentially beneficial effects on specific cognitive domains, particularly in symptomatic women and women who recently underwent menopause, as well as inadequate evidence of damage. Studies examining the cognitive effects of estrogen combined with progestogen on younger women are scarce[90].

In the WHIMS of Younger Women (WHIMSY), an ancillary study of the WHI study, the effect of HT (CEE/MPA, CEE-alone, and placebo) on cognition was evaluated in 1326 postmenopausal women aged 50 to 55 years. Cognitive testing was performed, on average, 7.2 years after the end of the WHI study, when participants had an average age of 67.2 years at their first evaluation. HT did not alter global cognitive function or the specific domains of cognition (verbal memory, working memory, verbal fluency, attention, and executive functions). WHIMSY data indicated that CEE-based HT administered to younger women in the initial postmenopausal period had no long-term beneficial or harmful effects[73]. Afterward, the authors published data from the extended follow-up accomplished through WHIMSY and WHIMS-Epidemiology of Cognitive Health Outcomes, in which HT was prescribed to women aged 65 to 79 years. The use of HT by younger women for up to 6 years had no significant effect on cognitive function in the long term. On the other hand, the use of HT for five years by older women was related to a decline in global cognitive function, executive functions, and working memory, which persisted for more than ten years after administration [91].

Another investigation that included younger women was the Cognitive Affective Study (KEEPS-Cog)[74], an ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS). The KEEPS-Cog studied the effects of HT administered for up to four years on cognition (global cognitive function, mental flexibility, verbal learning/memory, auditory attention, and executive functions) and humor in recently postmenopausal healthy women. In this randomized, double-blinded, placebo-controlled clinical trial, 0.45 mg of CCE was administered orally, plus 200 mg of micronized progesterone or 50 mcg of transdermal estradiol, plus 200 mg of micronized progesterone, as well as a placebo. Participants had a mean age of 52.5 years and were tested at an average of 1.4 years after menopause. HT did not affect cognition, and the use of oral CEE combined with micronized progesterone reduced anxiety and depressive symptoms, changes that were not observed in the group receiving transdermal therapy[74]. The KEEPS-Cog results regarding the lack of effect of HT on cognition are consistent with the WHIMSY findings.

The Early *vs* Late Intervention Trial with Estradiol (ELITE) was a randomized clinical trial in which participants received oral estradiol, micronized progesterone, or a matched placebo. The ELITE-Cog evaluated the effects of HT on cognition in postmenopausal women who were divided into two groups according to time since

menopause: early (less than six years, mean age of 55.6 years) or late (ten years or more, the mean age of 64.9 years). After an average of 57 mo of treatment, no significant differences in verbal memory, executive function, or global cognition were observed among women who initiated estradiol use within six years or ten years or more after menopause. These data suggest that estradiol has no beneficial or harmful effect on the evaluated cognitive domains, regardless of time elapsed since menopause; hence, the authors did not confirm the critical window hypothesis for cognitive function[92].

CONSIDERATIONS FOR CLINICAL PRACTICE

Clinical management of cognitive symptoms in perimenopausal women should consider that cognitive impairment does not appear to be frequent in this population [10], and an increased risk of dementia due to menopause is not well established[15,16, 18,19]. Nevertheless, patients with cognitive complaints and no objective impairment exhibited worse performance on cognitive tests than women without complaints[93]. Hence, some perimenopausal women might perceive the decline in verbal memory and learning performance compared to their ability during their premenopausal period, although they performed within normal parameters on neuropsychological tests[13]. Therefore, clinicians must validate the concerns about the cognitive decline of perimenopausal patients and evaluate their cognitive performance. Cognitive screening tests such as the MMSE[94] and the Montreal Cognitive Assessment (MoCA) [95], functional tests such as the Functional Assessment Questionnaire (FAQ)[96], and neurological examinations should comprise routine clinical evaluations. Due to the menopausal transition, cognitive symptoms are not expected to coincide with alterations on the MMSE, MoCA, FAQ, or neurological examination[97]. In these cases, patients should be advised that cognitive complaints are probably due to the menopausal transition associated with a subtle and transient cognitive decline[13]. Women with early menopause or those undergoing surgical or chemotherapy-induced menopause should be evaluated more carefully with repeated cognitive assessments during follow-up since these characteristics are more strongly associated with worse cognitive outcomes at older ages[15,20,21]. Scores less than 28 on the MMSE and less than 26 on the MoCA, indicating functional decline in daily activities (FAQ > 0), or altered neurological examinations are associated with cognitive impairment[98-100]. Notably, lower educational levels may bias cognitive tests, impairing their accuracy [101].

Suppose that screening tests indicate cognitive impairment in perimenopausal women. In that case, a comprehensive neuropsychiatric and neuropsychological assessment would be required to confirm the diagnosis of MCI or dementia in addition to a laboratory workup, neuroimaging examination, and, eventually, other tests to investigate underlying causes of cognitive decline. Thyroid hormones disturbances, vitamin B12 or folic acid deficiency, anemia, decompensated diabetes or hypoglycemia, electrolyte disturbances, renal or hepatic impairment, neurosyphilis or other infection of the central nervous system, and the use of benzodiazepines or medications with anticholinergic effects are potentially modifiable causes of cognitive impairment that should be excluded. Depression and other affective symptoms, such as anxiety, sleep disturbances, and attention deficit hyperactivity disorder, may exacerbate cognitive decline due to the menopausal transition, causing MCI in middle-aged women. In addition, presenile dementias such as familial AD, frontotemporal lobar degeneration, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy are uncommon neurocognitive disorders that may affect perimenopausal women.

Concerning the relationship between HT and cognition in postmenopausal women, the literature reports conflicting data. Notably, research differs in terms of the study design, age of the studied population, starting moment of HT, type, route of administration, and HT duration, among other aspects. An analysis of these studies allows us to verify dissonant findings, even among observational studies. Generally, observational studies have suggested some beneficial effects of HT on cognition, although some researchers, as previously described, have identified cognitive decline or an increased risk of dementia associated with HT. Regarding interventional studies, the findings are also not uniform concerning whether HT exerts detrimental or no effects on cognition. Overall, the results of interventional studies indicated detrimental effects of HT on older women, leading to cognitive decline and a greater risk of dementia, including AD.

Data on HT and cognition in younger postmenopausal women are scarce. Although observational studies suggest that HT may protect against future cognitive impairment in the early years of postmenopause, data from the WHIMSY trial[73,91], KEEPS-Cog trial[74], and ELITE-Cog trial[92] showed no benefits of HT in terms of the cognitive function of postmenopausal women compared to that of younger women. In younger symptomatic women, for whom benefits of using HT for symptom improvement have been reported, limited evidence suggests that these women do not appear to have a more significant risk of developing future cognitive problems.

Building big data and using data-driven approaches such as machine learning would help resolve conflicting data regarding the role of the menopausal transition in the risk of dementia and the effect of HT. In this context, big data may contribute to the prevention and early diagnosis of cognitive impairment in women undergoing the menopausal transition and facilitate evidence-based decision-making.

Based on the best available evidence, no robust data have been published that indicate that the use of HT with estrogen alone or combined with progestogen prevents cognitive decline or dementia in postmenopausal women. Thus, the prescription of HT is not recommended for this purpose.

CONCLUSION

The increasing number of people living with dementia will significantly impact life in years to come. Its effects will be felt individually, as it decreases the quality of life, both in patients and caregivers and at a population level, as it overburdens the health system and influences policies worldwide.

Being at greater risk of developing dementia, women are a target group of great interest for future studies. The link between sex and the risk of dementia still must be better understood. Along these lines, the menopausal transition is important, as it is a period of intense hormonal changes and symptomatic stress, which may be related to cognitive decline. Estrogen may play an essential role as a neuroprotective agent, although numerous other aspects are also relevant. A better understanding of the physiology involved in the cognitive impairment in this population, as well as the aspects of this decrease in cognition–which functions are affected and to what extent–may contribute to the elaboration of preventive measures and eventually may contribute to better treatment strategies, focusing on this possibly reversible cause of the cognitive decline.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 August 19; 11(8): 429-448

DOI: 10.5498/wjp.v11.i8.429

ISSN 2220-3206 (online)

REVIEW

Clozapine resistant schizophrenia: Newer avenues of management

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Author contributions: Chakrabarti S is the sole author of this manuscript.

Conflict-of-interest statement: No potential conflicts of interest.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: India

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

About 40%-70% of the patients with treatment-resistant schizophrenia have a poor response to adequate treatment with clozapine. The impact of clozapine-resistant schizophrenia (CRS) is even greater than that of treatment resistance in terms of severe and persistent symptoms, relapses and hospitalizations, poorer quality of life, and healthcare costs. Such serious consequences often compel clinicians to try different augmentation strategies to enhance the inadequate clozapine response in CRS. Unfortunately, a large body of evidence has shown that antipsychotics, antidepressants, mood stabilizers, electroconvulsive therapy, and cognitive-behavioural therapy are mostly ineffective in augmenting clozapine response. When beneficial effects of augmentation have been found, they are usually small and of doubtful clinical significance or based on low-quality evidence. Therefore, newer treatment approaches that go beyond the evidence are needed. The options proposed include developing a clinical consensus about the augmentation strategies that are most likely to be effective and using them sequentially in patients with CRS. Secondly, newer approaches such as augmentation with long-acting antipsychotic injections or multi-component psychosocial interventions could be considered. Lastly, perhaps the most effective way to deal with CRS would be to optimize clozapine treatment, which might prevent clozapine resistance from developing. Personalized dosing, adequate treatment durations, management of side effects and non-adherence, collaboration with patients and caregivers, and addressing clinician barriers to clozapine use are the principal ways of ensuring optimal clozapine treatment. At present, these three options could the best way to manage CRS until research provides more firm directions about the effective options for augmenting clozapine response.

Key Words: Clozapine-resistance; Augmentation; Medications; Electroconvulsive therapy; Psychosocial treatments; Schizophrenia

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Received: February 23, 2021
Peer-review started: February 24, 2021
First decision: March 30, 2021
Revised: April 12, 2021
Accepted: July 13, 2021
Article in press: July 13, 2021
Published online: August 19, 2021

P-Reviewer: Cheng J
S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Yuan YY

Core Tip: About 40%-70% of patients develop clozapine-resistant schizophrenia, which has serious health, economic, and social consequences. Research on clozapine-resistant schizophrenia has provided little support for the efficacy of psychotropics, electroconvulsive therapy, and cognitive-behavioural therapy in augmenting clozapine non-response. Therefore, newer approaches are needed including a clinical consensus about using the most effective of the currently available augmentation strategies. Augmentation with long-acting antipsychotic injections or multi-component psychosocial interventions could also be tried. Finally, the best option at present may be to prevent clozapine resistance from developing by optimizing clozapine treatment and collaborating with patients and caregivers to ensure its continuation.

Citation: Chakrabarti S. Clozapine resistant schizophrenia: Newer avenues of management. *World J Psychiatr* 2021; 11(8): 429-448
URL: https://www.wjgnet.com/2220-3206/full/v11/i8/429.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i8.429

INTRODUCTION

Although antipsychotic treatment is one of the principal options for the management of schizophrenia, about a third of the patients with schizophrenia do not respond well to first- or second-generation antipsychotics[1,2]. People with treatment-resistant schizophrenia (TRS) continue to have psychotic symptoms and functional impairment despite adequate antipsychotic use. TRS is associated with greater severity of symptoms, more frequent relapses, repeated hospitalizations, poorer socio-occupational functioning, and poorer quality of life(QOL). Consequently, it imposes a substantial economic and social burden on patients, families, and healthcare services[1,3]. Despite some contrary opinions, there is a widespread consensus that clozapine is the treatment of choice for patients with TRS[4,5]. However, even with optimal clozapine treatment, 40%-70% of the patients with TRS do not benefit from monotherapy with clozapine[6-9]. Patients with clozapine-resistant schizophrenia (CRS) are probably among the most severely ill of all patients with this disorder. A study comparing TRS and CRS found that the overall severity of the illness and positive and negative symptoms were significantly higher, while the QOL score was significantly lower among patients with CRS[10] Moreover, symptom severity among patients with CRS did not improve much over 6 mo of follow-up. Other estimates have suggested that apart from the greater symptom severity, patients with CRS are likely to be more frequent users of healthcare services and more likely to have multiple and prolonged hospitalizations[11].

Consequently, the cost of their care and the adverse impact of CRS on patients and their caregivers is also likely to be substantially greater than TRS[7,12]. Such serious consequences of CRS often compel clinicians to try new and different strategies to treat these patients. The option most commonly adopted is to add another psychotropic agent to clozapine to enhance its effects[9,11]. However, the evidence to date indicates that augmentation with medications or other treatments yields little or no additional benefits for these patients[13]. The treatment of CRS thus continues to pose a formidable challenge for clinicians. Moreover, the size of this group of patients will increase as the use of clozapine for TRS increases. Therefore, newer ways of managing CRS have to be explored. Accordingly, this review attempts to briefly summarize the research in this area, followed by a discussion of certain treatment options and strategies that appear promising.

DEFINING AND CONCEPTUALIZING CRS

The key elements of the current definitions of CRS are depicted in Table 1. These include a diagnosis of schizophrenia, moderate baseline severity, and non-response and persistence of symptoms, and functional impairment despite adequate treatment with clozapine[12,14-16]. Though these operationalized definitions of CRS represent an improvement, it is also apparent that the majority of clinical trials of patients with

Table 1 Key components of the current definitions of clozapine-resistant schizophrenia[12,14-16]

Diagnosis	Diagnosis of schizophrenia using standardized criteria and after ruling out psychosis due to substance use or medical conditions
Adequate clozapine treatment	
Dose	200-500 mg/d
Blood levels	≥ 350 ng/mL
Treatment duration	2-3 mo[1]
Treatment adherence	≥ 80% of prescribed doses for the duration of treatment
Response to clozapine	
Baseline symptom severity and functional impairment	Moderately severe illness either globally or in positive and negative symptom domains assessed using standardized scales (CGI, BPRS, PANSS, SAPS, SANS). Moderate levels of functional impairment assessed using standardized scales (GAF, SOFAS)
Non-response	< 20% reduction in symptoms and minimal response in levels of functional impairment during an adequate trial of clozapine treatment
Persistence	Moderately severe illness and functional impairment should persist following an adequate trial of clozapine treatment

[1]It has been proposed that duration of clozapine trials should be 2 mo for patients with aggression or self-harm, 3 mo for those with positive symptoms, and 4 mo for those with negative and cognitive symptoms[13].

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression scale; GAF: Global Assessment of Functioning scale; PANSS: Positive and Negative Syndrome Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SOFAS: Social and Occupational Functioning Scale.

CRS have not utilized such definitions. Moreover, a major criticism of the current constructs of CRS is that they rely excessively on positive symptoms of schizophrenia [11,17,18]. Other domains such as negative, cognitive, or depressive symptoms, or QOL have not received sufficient attention. This gives rise to substantial heterogeneity in the CRS groups selected using such definitions, which further hinders research. Although measures such as more precise delineation of target symptoms and differentiating between "minimum and optimal criteria" required for CRS have been proposed [15,16], the current definitions are still far from perfect[11,15,18,19]. Finally, from a clinical perspective there are many practical difficulties in determining adequate doses, estimating blood levels, judging adherence, and conducting prospective observation of patients during treatment with clozapine[15,16].

AUGMENTATION STRATEGIES FOR CRS: A BRIEF REVIEW

Medication augmentation

In routine clinical practice, the commonest strategy to deal with CRS is augmentation with another antipsychotic[9,11,20,21]. Mood stabilizer or antidepressant augmentation is used less frequently. Some treatment guidelines also endorse augmentation with antipsychotics[13]. Over the past 25 years, many trials of clozapine augmentation with medications and other treatments have been conducted. Additionally, more than 50 reviews on the subject including narrative and systematic reviews, individual meta-analyses, and reviews of different meta-analyses have been published.

Antipsychotic augmentation: Some of the recent reviews of augmentation of clozapine with a second antipsychotic in CRS are included in Table 2[22-44].

Among all augmentation trials, the largest number has involved antipsychotic augmentation of clozapine non-response. Risperidone, aripiprazole, and amisulpride are the most commonly evaluated augmenting agents. Despite the size of the evidence, the majority of reviews have concluded that adding a second antipsychotic to clozapine does not have any significant impact on clinical response, overall symptom severity, or severity of positive symptoms[7,8,20,45,46]. Though some benefit has been noted when all trials are included, there appear to be no significant effects when only high-quality trials are considered[2,18]. Even when benefits are evident in well-designed randomized controlled trials (RCTs), the combined effect sizes are small to moderate casting doubts on the clinical significance of these findings. The effect of antipsychotic combinations with clozapine on negative and depressive symptoms has

Table 2 Reviews of antipsychotic augmentation strategies in clozapine-resistant schizophrenia[1]

Ref.	Type of review	Details	Effect on positive or psychotic symptoms	Effect on negative or depressive symptoms
Wagner *et al* [2], 2019	Systematic review	14 meta-analyses of FGA and SGA augmentation of clozapine.	Some evidence of benefits based on low-quality studies (SIGN grade B).	
Roerig *et al* [8], 2019	Systematic review	4 meta-analyses and 1 naturalistic study of FGA and SGA augmentation of clozapine.	No benefits of antipsychotics when high-quality RCTs were considered.	
Bartoli *et al* [22], 2019	Meta-analysis	12 RCTs of SGA augmentation of clozapine-risperidone (n = 5) and aripiprazole (n = 3).	No difference between SGA augmentation and placebo in improving positive symptoms.	A small benefit of SGA augmentation for negative and depressive symptoms.
Siskind *et al* [23], 2018	Meta-analysis	19 RCTs of FGA and SGA augmentation of clozapine-aripiprazole (n = 7), risperidone (n = 3), and amisulpiride (n = 2).	Evidence for benefit with aripiprazole, but effects were lost when low-quality studies were excluded.	
Correll *et al* [24], 2017	Meta-analysis	Meta-analysis of 29 previous meta-analyses of antipsychotic combinations-5 clozapine combinations examined.	Clozapine combinations no different from clozapine monotherapy for positive symptoms.	Clozapine combinations no different from clozapine monotherapy for negative symptoms.
Galling *et al* [25], 2017	Meta-analysis	20 RCTs of FGA and SGA augmentation of clozapine-risperidone (n = 6) and aripiprazole (n = 6).	No evidence for additional benefits of augmentation in double-blind, high-quality RCTs.	Improvement in negative symptoms with aripiprazole augmentation. No effect of augmentation on depressive symptoms.
Ortiz-Orendain *et al*[26], 2017	Meta-analysis	31 RCTs and quasi-RCTs of augmentation with SGAs (n = 26) and FGAs (n = 5) including clozapine augmentation.	Low-quality evidence that augmentation improves global clinical response. No specific effects on positive symptoms.	No effect of augmentation on negative symptoms.
Barber *et al* [27], 2017	Meta-analysis	5 RCTs of clozapine augmentation with SGAs or haloperidol.	Low-quality evidence that augmentation may improve global clinical response. Effects on positive symptoms not clear.	Effects on negative symptoms not clear.
Jiménez-Cornejo *et al* [28], 2016	Meta-analysis	17 prior meta-analyses and reviews of FGA and SGA augmentation (62 studies) of clozapine.	Little evidence that augmentation improves clinical response (> 20% reduction in PANSS/BPRS scores).	
Taylor *et al* [29], 2012	Meta-analysis	14 RCTs of FGA and SGA augmentation of clozapine.	A small benefit in overall symptom reduction with augmentation.	
Sommer *et al* [30], 2012	Meta-analysis	10 RCTs of FGA and SGA augmentation of clozapine.	One RCT showed that sulpiride augmentation led to overall symptom reduction. No specific effects on positive symptoms.	No specific effects on negative symptoms.
Porcelli *et al* [31], 2012	Systematic review and meta-analysis	Systematic review of 25 studies of SGA augmentation of clozapine - risperidone (11 trials) and aripiprazole (6 trials). Meta-analysis of 5 RCTs of risperidone augmentation of clozapine.	Low quality evidence indicated benefits for aripiprazole and amisulpiride augmentation. No benefit of risperidone augmentation.	Some benefit of aripiprazole in reducing negative symptoms from 1 RCT.

[1]Several other systematic reviews[9,12,14,32,33] and meta-analyses[17,34-37] have been unable to find significant benefits, while others have reported modest benefits for antipsychotic augmentation of clozapine[38-44].

BPRS: Brief Psychiatric Rating Scale; FGA: First-generation antipsychotic; RCT: Randomized controlled trial; PANSS: Positive and Negative Syndrome Scale; SGA: Second-generation antipsychotic; SIGN: Scottish Intercollegiate Guidelines Network.

been examined less frequently. A similar inconsistency is apparent with some meta-analyses showing modest benefits, while others report no effects on these symptoms.

Antidepressant and mood stabilizer augmentation: As depicted in Table 3, the number of RCTs examining the augmentation of clozapine with antidepressants and mood stabilizers is comparatively less. Moreover, the trials are more often of poorer quality. Consequently, there is little evidence of the benefits of antidepressant augmentation on the severity of symptoms[23,24,30,37]. When some evidence of a positive effect has been found, it is usually based on single, high-quality RCTs[23,24,30,37]. Similarly, though mood stabilizer augmentation is reported to be beneficial in some meta-analyses[47,48], others have either found no benefit[7,24,46,49] or evidence of significant symptom reduction only in low-quality trials[2,8,23,30,50].

Table 3 Meta-analyses of antidepressant and mood stabilizer augmentation in clozapine-resistant schizophrenia

Ref.	Type of review	Details	Results
Antidepressants			
Siskind *et al* [23], 2018	Meta-analysis	10 RCTs of fluoxetine, paroxetine, duloxetine, and mirtazapine augmentation	Some evidence for fluoxetine augmentation in reducing in overall symptom severity based on 1 high-quality RCT.
Correll *et al* [24], 2017	Meta-analysis	Analysis based on the earlier meta-analysis of Veerman *et al*[37]	No benefit of antidepressant augmentation on reduction in overall, positive, and negative symptom severity.
Veerman *et al* [37], 2014	Meta-analysis	4 RCTs of mirtazapine, duloxetine, and fluoxetine augmentation	No benefit of antidepressant augmentation on reduction in overall, positive, and negative symptom severity.
Sommer *et al* [30], 2012	Meta-analysis	4 RCTs of mirtazapine, citalopram, and fluoxetine augmentation	Some evidence for citalopram augmentation in reducing overall and negative symptom severity based on 1 RCT.
Mood stabilizers			
Siskind *et al* [23], 2018	Meta-analysis	5 RCTs of valproate (n = 2), lamotrigine (n = 2), lithium (n = 1), and topiramate(n = 1) augmentation	Low-quality evidence for valproate and lithium augmentation in reducing total symptom severity. Reduction of positive and negative symptom severity by topiramate augmentation based on1 RCT.
Correll *et al* [24], 2017	Meta-analysis	Analysis based on the earlier meta-analysis of Veerman *et al*[37]	No benefit of lamotrigine and topiramate augmentation on reduction in overall, positive, and negative symptom severity.
Zheng *et al* [50], 2017	Meta-analysis	22 RCTs of valproate (n = 9), lamotrigine (n = 8), and topiramate (n = 4) augmentation	Significant benefits for valproate and topiramate in reducing total and positive symptom severity but based on low-quality studies. No effects on clinical response.
Zheng *et al* [48], 2016	Meta-analysis	4 RCTs of topiramate augmentation	Significant benefits of topiramate augmentation in reducing overall, positive, and negative symptom severity.
Veerman *et al* [49], 2014	Meta-analysis	6 RCTs of lamotrigine and 4 RCTs of topiramate augmentation	No benefit of lamotrigine and topiramate augmentation on reduction in overall, positive, and negative symptom severity.
Sommer *et al* [30], 2012	Meta-analysis	7 RCTs of lamotrigine (n = 4) and topiramate (n = 3) augmentation	Benefits of lamotrigine and topiramate augmentation for total and positive symptoms based on single RCTs that did not persist on further analysis.
Tiihonen *et al* [47], 2009	Meta-analysis	5 RCTs of lamotrigine augmentation	Evidence for benefit of lamotrigine augmentation in reducing overall, positive, and negative symptom severity.

RCT: Randomized controlled trial.

Methodological lacunae: One of the principal reasons for the inability to find effective medication augmentation options for CRS is the methodological shortcomings of current research. Even in the better quality RCTs, there is considerable heterogeneity in terms of the definitions used, the types and numbers of patients included, the duration of trials, and the outcomes examined. The methodological lacunae of the RCTs have in turn affected the methodological quality of meta-analytic examinations of the evidence. For example, in a systematic review of 21 meta-analyses only one was judged to have "very little risk of bias;" 7 had "low risk of bias," and the rest had "high risk of bias"[2]. Therefore, there is considerable uncertainty even about the findings of meta-analytic studies.

Augmentation with electroconvulsive therapy and recurrent transcranial magnetic stimulation

Some of the more recent reviews have concluded that electroconvulsive therapy (ECT) is an effective augmentation strategy, especially when medications fail to decrease persistent positive symptoms[2,8,20,46,51]. However, this conclusion appears to be based on a single meta-analysis of 18 RCTs[52], which showed that the ECT-clozapine combination was better than clozapine alone in reducing positive symptoms. Then again, 17 of these RCTs were conducted in China and are not easily accessible[53]. As shown in Table 4, there are only two small RCTs of ECT augmentation of clozapine response. The first showed that the clozapine-ECT combination was more effective than clozapine alone in TRS[54], whereas the second did not find the combination to be more effective in CRS[55]. The rest of the evidence consists of non-randomized trials[56] and case studies. Thus, the higher response rates of the clozapine-ECT combination reported in systematic reviews[57-61] and other meta-analyses[62-64] are largely based on low-quality evidence, obtained mainly among patients with TRS, and

Table 4 Electroconvulsive therapy and recurrent transcranial magnetic stimulation augmentation in clozapine-resistant schizophrenia

ECT			
Ref.	**Study/review**	**Details**	**Results**
Masoudzadeh *et al*[56], 2007	Controlled trial, (non-randomized, non-blinded)	18 patients with TRS; 3 groups of clozapine-ECT treatment, only clozapine and only ECT treatment (n = 6 each)	Significant differences between the clozapine- ECT combination and monotherapy groups in reduction of PANSS scores.
Petrides *et al*[54], 2015	Single-blind cross-over RCT	39 patients with TRS randomized to clozapine-ECT (n = 20) and clozapine only treatment (n = 19)	Significantly greater response on BPRS psychosis & CGI scores in the clozapine-ECT combination group.
Melzer-Ribeiro *et al*[55], 2017	Single-blind sham-controlled RCT	23 patients with CRS randomized to treatment with clozapine-ECT (n = 13) and clozapine-sham ECT (n = 10)	No significant differences between the groups on PANSS total and positive symptom scores and CGI scores.
Kupchik *et al*[57], 2000	Systematic review	Case reports of 36 patients with TRS and clozapine non-responders	67% of the patients on the clozapine-ECT combination showed good response.
Braga *et al*[58], 2005	Systematic review	12 case reports or chart reviews of patients with TRS and clozapine non-responders	The clozapine-ECT combination was efficacious.
Havaki-Kontaxaki *et al*[59], 2006	Systematic review	One open trial and 6 case studies of patients with CRS	73% patients on the clozapine-ECT combination showed marked improvement.
Pompili *et al*[60], 2013	Systematic review	31 studies examining indications for ECT in schizophrenia	The clozapine-ECT combination was efficacious in patients resistant to medications.
Grover *et al*[61], 2015	Systematic review	40 studies, mainly case reports of patients with CRS	Short-term response rates of the clozapine-ECT combination varied from 37%-100%.
Lally *et al*[62], 2016	Systematic review and meta-analysis	Pooled analysis of patients with TRS treated with clozapine and ECT based on 4 open trials, 2 controlled trials (1 RCT)[1], 2 chart reviews, 6 case series, and 15 case reports	Pooled response rate with the clozapine-ECT combination was 54% on meta-analysis. Systematic review showed 76% overall response rate with clozapine-ECT treatment and a relapse rate of 32%.
Manubens *et al*[63], 2016	Systematic review and meta-analysis	6 systematic reviews of ECT in TRS including 6 controlled trials of the clozapine-ECT combination in clozapine non-responders (1 RCT)[1]	Modest effect of ECT in augmenting clozapine response with low certainty of evidence.
Ahmed *et al*[64], 2017	Systematic review and meta-analysis	9 studies of the clozapine-ECT combination in TRS including 2 controlled trials (1 RCT)[1], 3 open trials, and 4 case series/chart-reviews *vs* 9 studies of ECT-non-clozapine antipsychotic combination	The ECT-clozapine combination was significantly better than the ECT-non-clozapine antipsychotic combinations in reducing positive symptoms on the PANSS and the BPRS.
Wang *et al*[52], 2018	Meta-analysis	18 RCTs of clozapine augmentation in CRS (17 from China and 1 from the United States[1])	Adjunctive ECT was superior to clozapine monotherapy in reducing positive symptoms after 1–2 wk but with moderate effect size.
rTMS			
Wagner *et al*[66], 2020	Meta-analysis	Pooled data from 10 RCTs for 131 patients with persistent positive and negative symptoms being treated with clozapine	No differences between active and sham rTMS in improving clinical response and reducing PANSS scores. No benefit of rTMS augmentation for patients with persistent symptoms on clozapine.

[1]The RCT from United States is by Petrides *et al*[54].

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression scale; CRS: Clozapine-resistant schizophrenia; ECT: Electroconvulsive therapy; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized controlled trial; rTMS: Recurrent transcranial magnetic stimulation; TRS: Treatment resistant schizophrenia.

limited to the short-term efficacy of ECT augmentation. Though the combination appears to be relatively safe, about 20% of the patients develop adverse effects, and there is some evidence of greater cognitive impairment[52,57,59,62,63]. Nevertheless, augmentation with ECT may result in a faster response, which is particularly useful among patients with high risks of aggression or self-harm[9,11,60,65]. Therefore, though the evidence is still inconclusive, the effects of ECT augmentation certainly merit further examination. On the other hand, augmentation with recurrent transcranial magnetic stimulation appears to be largely ineffective in CRS despite promising results from recent trials[66,67].

Psychosocial augmentation strategies

Two systematic reviews of psychosocial interventions have concluded that CBT can be effective among patients with poor response to clozapine[33,68]. As shown in Table 5, the evidence-base for CBT until recently had consisted of a few trials with small

Table 5 Psychosocial augmentation strategies in clozapine-resistant schizophrenia

Ref.	Study/participants	Interventions	Results
Studies			
Pinto *et al*[69], 1999	Single-blind RCT of 41 patients with TRS started on clozapine	CBT and social skills training *vs* supportive therapy for 6 mo.	Significant reductions in positive and negative symptom severity in the CBT group.
Buchain *et al*[70], 2003	Single-blind RCT of 41 patients with TRS started on clozapine	Occupational therapy and clozapine *vs* clozapine alone for 6 mo.	Significant improvements in the occupational performance and interpersonal relationships with OT.
Barretto *et al*[71], 2009	Single-blind RCT of 21 patients with CRS	CBT *vs* supportive treatment ("befriending") for 21 wk.	Significant reductions in overall symptom severity and improvement in quality of life with CBT.
Morrison *et al*[75], 2018	Double-blind RCT of 425 patients with CRS	CBT *vs* usual treatment for 9 mo. Follow-up for 21 mo.	Significant reductions in PANSS scores with CBT at 9 mo but no differences at 21 mo.
Sensky *et al*[72], 2000; Valmaggia *et al*[73], 2005; Edwards *et al*[74], 2011	RCTs of patients with TRS (n = 48-90) including patients on clozapine or clozapine non-responders	CBT *vs* supportive treatment or clozapine alone or comparisons with combinations of CBT with other antipsychotics.	Significant reductions in positive, negative, and depressive symptom severity, improvement in clinical response and functioning with CBT; benefits at end of treatment usually maintained during follow-up.
Reviews			
Ranasinghe *et al*[33], 2014	Systematic review	Review of the 2 CBT and 1 OT trial mentioned above.	Benefits of psychosocial interventions noted for overall symptom severity, quality of life, and social functioning.
Polese *et al*[68], 2019	Systematic review & meta-analysis	Review of all the above trials and meta-analysis of 4 RCTs including Morrison *et al*[75].	Benefits of psychosocial interventions noted for overall and positive symptom severity.

CBT: Cognitive-behavioural therapy; CRS: Clozapine resistant schizophrenia; PANSS: Positive and Negative Syndrome Scale; OT: Occupational therapy; TRS: Treatment resistant schizophrenia; RCT: Randomized controlled trial.

numbers and inadequate study designs[69-71] or RCTs that included some patients with CRS[72-74]. However, interest in the effects of CBT augmentation has been re-awakened with a large, well-designed RCT among patients with CRS[75]. This was the largest trial among all RCTs of clozapine augmentation. It employed standardized definitions of CRS and trained therapists who administered manual-based CBT to patients from routine clinical settings. After 9 mo of active treatment, the total Positive and Negative Symptom Scale scores, positive symptoms, emotional distress, and excitement had reduced significantly in the CBT group compared to the usual treatment group. However, at the end of 21 mo, there were no significant differences in the Positive and Negative Symptom Scale scores between the two groups, leading to the conclusion that CBT augmentation was not effective in CRS. Nevertheless, other indices suggested that CBT might be useful for a proportion of patients, and patients' ratings of recovery were greater in the CBT group at 21 mo. Other noteworthy advantages of CBT were the high adherence rates, negligible adverse effects, high acceptability, and effect sizes comparable to medication augmentation. Therefore, others have interpreted these results differently to emphasize the positive effects of CBT augmentation[2,66,76]. Moreover, it has been pointed out that the persistence of positive effects beyond the active treatment period is not the best indicator of the efficacy of CBT[76]. Thus, if the standards for medication trials were to be applied to this RCT, the conclusion would be that CBT was an effective augmentation strategy for CRS after 9 mo of treatment.

AUGMENTATION STRATEGIES FOR CRS: FROM EVIDENCE TO PRACTICE

Relying on clinical consensus

This brief update of the existing literature shows that augmentation of clozapine response in CRS with medications, ECT, or CBT is largely ineffective. Any favourable outcome for augmentation is usually based on low-quality or limited evidence, and the clinical significance of the small effects obtained in some meta-analyses is unclear. Moreover, because of the inconsistent results and methodological uncertainties, the

evidence offers no definite conclusions about the most effective augmentation strategies. Nevertheless, it has been suggested that the lack of evidence should not discourage clinicians from trying out these strategies in individual patients. This advice appears to be based on two assumptions. First, the lack of significant benefits applies only to entire groups of patients being evaluated in RCTs, whereas there may be considerable variability in individual responses of the patients comprising these groups[18,25,29,40]. Thus, there is a possibility that some patients may benefit from augmentation, though at present there is no way to identify these potential responders. Moreover, given the widespread adverse impact of CRS, even modest benefits are considered acceptable in clinical settings[7,22,46]. Therefore, the sequential use of different augmentation strategies is considered to be a realistic option in clinical practice.

To reduce the disparity between the evidence-based findings and clinical practice, researchers have been increasingly relying on clinical consensus to guide the management of complex and burdensome conditions such as CRS. A recent effort on these lines arrived at the following recommendations for augmentation of clozapine non-response: personalizing doses to reach plasma levels ≥ 350 ng/mL; a 3 mo trial for patients with positive symptoms; shorter treatment trials for those with violence or self-harm (2 mo) and longer periods (4 mo) for patients with negative or cognitive symptoms[13]. For persistent positive symptoms, adding aripiprazole, amisulpride, or ECT was suggested. Augmentation with antidepressants was recommended for negative symptoms while adding antidepressants, antipsychotics, mood stabilizers, or ECT to clozapine was proposed for CRS with increased risks of aggression or self-harm. Lastly, CBT or other psychosocial interventions were also felt to be useful. It was apparent that these clinicians were going beyond the current evidence while making some of these recommendations.

For example, though there is little support in the literature for augmentation of clozapine with a second antipsychotic, low-quality evidence or single RCTs have suggested that risperidone, aripiprazole, and amisulpride may be beneficial (Table 2). The group also relied on naturalistic studies showing that the clozapine-aripiprazole combination may have positive effects[77]. Similarly, for recommendations about antidepressants, positive evidence for antidepressant augmentation in schizophrenia was cited[78,79], though the evidence for similar effects of antidepressant augmentation in CRS is limited (Table 3).

Augmentation with mood stabilizers and ECT was recommended despite the acknowledgement that the evidence for these strategies is insufficient (Tables 3 and 4). The recommendation for using CBT if other treatments failed was based on the recent CBT trial[75], which concluded that certain individuals with CRS may benefit from a practical trial of CBT augmentation. Clozapine augmentation was preferred over a switch to a different antipsychotic because of the consistent evidence of adverse outcomes following cessation of clozapine[8,11,80-82]. Switching to high-dose olanzapine has been suggested as an alternative, but this option is not supported by evidence[81,83]. Finally, though most of the evidence indicates that these augmentation strategies are safe and well-tolerated[22,25,26,29], the possibility of new side effects arising during combined treatment could not be discounted[9,12,18,28,32]. Therefore, cautious monitoring of all patients for the duration of the augmentation trial was also recommended.

Trying newer options for augmentation

Augmentation with long-acting antipsychotic injections: Apart from problems of resistance, non-adherence is a major hindrance to effective treatment with clozapine. Although non-adherence with clozapine may be lower than other antipsychotics, rates of intentional non-adherence vary from 23%-55% during treatment[84-88]. In such situations initiating a long-acting antipsychotic injection (LAI) remains the only option [89]. Intramuscular clozapine appears to have some benefits in enhancing adherence, but it has not been used frequently[90,91]. Recent studies suggest that apart from reducing non-adherence, LAI augmentation of clozapine may also have a role in enhancing clozapine response in CRS. As shown in Table 6, this evidence is still preliminary and consists mostly of series of patients and observational studies[92-102]. However, mirror-image studies that are considered the current standard for evaluating LAI efficacy[103,104] have also been conducted. Taken together, this body of evidence suggests that the combination of clozapine with LAIs leads to a reduction in all types of symptoms and behavioural problems such as aggression and suicidality as well as improvements in social functioning. The lowered risk of relapses and reduction in the number and length of hospitalizations has also been replicated consistently. Lastly, it appears that lower doses of both medications are required,

Table 6 Augmentation of clozapine with long-acting antipsychotic injections in clozapine-resistant schizophrenia

Ref.	Study details	Results
Kim *et al*[92], 2010	4 patients treated with clozapine and risperidone LAI for 1 yr	Reduction in number and length of hospitalizations and improvement in social skills after LAI addition. Fewer side effects with the combination.
Malla *et al*[93], 2013	One patient with poor response to clozapine treated with clozapine and an LAI	Improvement in symptoms and social functioning without any increase in side effects with combination treatment.
Baruch *et al* [94], 2014	8 patients, 6 with TRS. Treated with olanzapine LAI and clozapine or other antipsychotics up to 2 yr	Reduction in aggression in all 8 patients and in symptom severity in 6 patients.
Maia-de-Oliveira *et al* [95], 2015	2 patients with CRS treated with clozapine and paliperidone LAI for 9-10 mo	Remission of positive symptoms after LAI augmentation.
Kasinathan *et al* [96], 2016	9 patients with TRS and comorbid personality disorders/substance use and violence; 1 on clozapine but non-adherent treated with olanzapine LAI combination	1 yr of retrospective pre- and post-LAI comparisons showed significant improvements in psychotic symptoms, violence, and reduction in number and length of hospitalizations and emergency visits.
Sepede *et al* [97], 2016	One patient with poor response to clozapine treated with clozapine and aripiprazole LAI for 1 yr	Symptoms reduced by 50% with the combination without any increase in side effects.
Oriolo *et al*[98], 2016	Retrospective observational of 23 patients with TRS in whom paliperidone LAI was added toclozapine	Significant reductions in severity of global, positive, negative, depressive, and cognitive symptoms with the combination. Significantly lower doses of clozapine and paliperidone LAI required with combination treatment *vs* monotherapy.
Souaiby *et al* [99], 2017	Retrospective observational study with a mirror-image design of 20 patients with TRS treated with clozapine and LAIs for 32 mo	Significant reductions in number and length of hospitalizations during 32 mo of combination treatment *vs* 1 yr of monotherapy. No increase in side effects with the combination.
Grimminck *et al* [100], 2020	Retrospective observational study with a mirror- image design of 20 patients with poor response to clozapine or LAIs treated with clozapine and LAI combinations for 2 yr	Significant reductions in hospital admissions and emergency visits during 2 yr of combination treatment *vs* 2 yr of monotherapy. Overall improvement in behaviour and social functioning but no change in symptoms.
Bioque *et al* [101], 2020	Retrospective observational study with a mirror- image design of 50 patients with TRS treated with clozapine and paliperidone LAI for 6 mo	Significant reductions in BPRS scores, emergency visits, number and length of hospitalizations, and number and severity of adverse effects as well as significant improvements in social functioning during 6 mo of combination treatment *vs* 6 mo of monotherapy.
Caliskan *et al* [102], 2021	Retrospective observational study with a mirror- image design in 29 patients with TRS treated with clozapine and LAI combinations for 1 yr	Significant reductions in number of relapses and number and length of hospitalizations during 1 yr of combination treatment *vs* 1 yr of monotherapy. No differences in side effects with the combinations.

BPRS: Brief Psychiatric Rating Scale; CRS: Clozapine resistant schizophrenia; LAI: Long-acting antipsychotic injection; TRS: Treatment resistant schizophrenia.

while side effects are either less, or no more common with the combination than with clozapine monotherapy.

Indirect evidence for the effectiveness of clozapine-LAI combinations also comes from several Scandinavian nationwide cohort studies of antipsychotic treatment summarized in Table 7[77,82,105-109]. These provide the strongest support for the notion that clozapine and LAIs are the two most effective treatments for patients with both first episode and chronic schizophrenia. Incidentally, some of these studies have also shown that the combination of clozapine and aripiprazole is more effective than clozapine monotherapy[77]. Therefore, the combination of clozapine and LAIs appears to be a promising option that needs to be examined further for its usefulness in the management of CRS.

A re-evaluation of psychosocial augmentation strategies: Although the evidence reviewed in Table 5 suggests that augmentation with CBT does not yield consistent benefits in CRS, there are several reasons to re-examine the usefulness of psychosocial augmentation strategies. To begin with, CBT augmentation appears to be effective for persistent positive symptoms in TRS[20,68,75,76]. Moreover, the largest and most meticulously conducted CBT trial has shown a small but significant benefit for patients with CRS following the active intervention phase[66,75,76]. The same trial has suggested that CBT is one of the safest and acceptable augmentation options for patients with CRS. The evidence from this study and other trials shows that CBT augmentation has added benefits such as improvements in socio-occupational functioning and QOL. Moreover, symptomatic remission appears to be faster with CBT augmentation, and the benefits obtained may persist longer[71,72,74]. CBT augmentation early in the course of clozapine treatment may further enhance its benefits[68-70,74].

Table 7 Scandinavian nationwide cohort studies of antipsychotic treatment

Ref.	Study details	Results
Tiihonen *et al* [105], 2006, Finland	2230 inpatients followed up for 3.6 yr	Significantly lower risks of rehospitalization or treatment discontinuation in patients on perphenazine LAI, clozapine, or olanzapine *vs* those on oral haloperidol.
Tiihonen *et al* [106], 2009, Finland	66881 outpatients followed up for 11 yr	Clozapine was associated with a substantially lower mortality than any other antipsychotics singly or in combination, with perphenazine as a comparator.
Tiihonen *et al* [107], 2011, Finland	2588 inpatients followed up for 2 mo after discharge	Significantly lower risks of rehospitalization with LAIs than oral medications. Clozapine and olanzapine were associated with significantly lower risk of rehospitalization than risperidone.
Tiihonen *et al* [108], 2017, Sweden	29823 patients followed up for 5.7 yr	Significantly lower risks of rehospitalization and of treatment failure[1] with LAIs and clozapine *vs* no antipsychotic treatment.
Taipale *et al* [109], 2018, Finland	62250 inpatients followed up for 20 yr	Significantly lower risks of rehospitalization with LAIs and clozapine *vs* no antipsychotic treatment in first episode and chronic schizophrenia.
Tiihonen *et al* [77], 2019, Finland	62250 inpatients on antipsychotic monotherapy or antipsychotic combinations followed up for 14 yr	Combination of clozapine and aripiprazole was associated with significantly lower risk of rehospitalization and mortality than clozapine alone in first episode and chronic schizophrenia. Clozapine monotherapy was associated with the most favourable outcomes compared to other antipsychotics.
Luykx *et al*[82], 2020, Finland	2250 patients on clozapine treatment followed up for more than 1 yr before discontinuation	Compared to no antipsychotic treatment, significantly lower risks of rehospitalization with re-institution of clozapine alone, oral olanzapine, and antipsychotic combinations. Significantly lower risks of treatment failure**1**with aripiprazole LAI, re-institution of clozapine alone, and oral olanzapine.

[1]Treatment failure included re-hospitalization, suicide attempt, treatment discontinuation, medication switch, or death.
LAI: Long-acting antipsychotic injection.

Further, it has been proposed that rather than using only CBT, multi-component psychosocial interventions using different techniques might be more effective in enhancing clozapine response[33,110,111]. Though CBT is the most common psychosocial treatment used in patients with TRS, there is evidence to suggest that other types of interventions might be equally effective[68,112]. Psychoeducation and family interventions are also effective for schizophrenia[113], but they have not been tried out as augmenting strategies in TRS or CRS[20,68]. Lastly, psychosocial aug-mentation might be useful in other ways, for example in improving adherence to clozapine. An RCT that compared CBT with psychoeducation among patients with TRS on clozapine showed that both treatments led to improvements in patient empowerment, treatment alliance, and medication persistence[114]. Thus, while there may be no compelling evidence in favour of psychosocial augmentation strategies in CRS, there is scope for further evaluation of these potentially useful treatments.

PREVENTING RESISTANCE TO CLOZAPINE TREATMENT

The relative ineffectiveness of the different augmentation strategies suggests that a more fruitful option could be to try and prevent resistance to clozapine treatment from developing.

Predicting clozapine resistance

Predicting who among patients with TRS will not respond adequately to clozapine may be helpful because augmentation strategies could be instituted early in such patients to mitigate the adverse effects of clozapine resistance. However, despite over 300 studies of prediction of clozapine response, consistent predictors of response have not been found. Some reviews have concluded that there are no reliable predictors of clozapine response because of the inconsistent results and methodological uncertainties of existing research[115,116]. On the other hand, an older systematic review and a more recent meta-analysis have found that older age, greater severity of symptoms, especially negative symptom severity, poorer functioning, and non-paranoid subtypes could predict clozapine non-response[117,118]. Low cerebrospinal homovanillicacid to 5-hydroxyindoleacetic acid ratios and normal structure and

function of the prefrontal cortex have also emerged as reliable predictors of good response in some studies[117,119]. Consequently, because of the inconclusive nature of this evidence, currently the only way to predict clozapine resistance is to carry out an adequate trial of clozapine treatment under optimal conditions[20,115].

Optimizing clozapine treatment

Ensuring adequate treatment with clozapine may thus be the best option to prevent clozapine resistance. The necessary steps for optimizing clozapine treatment are listed in Table 8. Personalized dosing is a key component because of the wide variations in dose-blood level ratios between individuals and because many patients respond at lower doses[120,121].

Data on gender differences in clozapine treatment are scarce, and results are often inconsistent[122]. This is particularly true for response to clozapine treatment. Though the response is usually poorer in women[116,117,122], research on clozapine's effectiveness has also found better outcomes among women, although these differences in their favour are often of doubtful clinical significance[115,117,123]. Others have found no differences in outcome between the two genders[118].

In contrast, differences in pharmacokinetics are reported more consistently[122,124,125]. Women have lower renal clearance of clozapine than men because of differences in the activity of cytochrome P450 enzymes such as CYP1A2. Most studies have found higher plasma levels of clozapine in women, and some have also found higher levels of its metabolite norclozapine. Higher dose-blood level ratios have also been found in women. Therefore, women usually require lower doses of clozapine[124]. These pharmacokinetic differences also increase the risk of dose-dependent side effects in women, particularly metabolic side effects[122,126]. Accordingly, most of the evidence on gender differences in side effects of clozapine relates to metabolic disturbances [122]. However, findings are not consistent, and both genders appear to have increased risk of metabolic syndrome in different reports[122,126-128]. Hypertension, elevated triglycerides, lower high-density lipoprotein levels, and cardiac abnormalities appear to be more common in men[122]. Women are more likely to develop hyperglycaemia and diabetes and increases in weight and body mass index[122,126]. There is very little evidence of gender differences in other side effects, though certain studies have found haematological abnormalities and constipation to be commoner among women[122,125,128,129].

Unlike the influence of gender, ethnicity does not appear to have any impact on treatment response obtained with clozapine[115,130]. On the other hand, there are ethnic differences in pharmacokinetic profiles of clozapine[122]. More specifically, several studies among Asian patients have consistently indicated that they require about half the standard dose of clozapine due to their lowered clozapine metabolism [131-135]. The dose of clozapine required for adequate response among Asians varies from 150mg/d among women to 300 mg/d for men who smoke. Therefore, Asian patients need lower doses at the start of treatment and slower upward titration to reach their optimum dose. Despite these pharmacokinetic dissimilarities, ethnic differences seem to have minimal impact on the prevalence of adverse effects of clozapine[129]. Nevertheless, non-White ethnicity is a risk factor for metabolic syndrome, and certain studies have found a higher prevalence of hypertension and weight gain in Asians[127,136]. Others have found a higher risk of agranulocytosis in Asian patients[137]. This again emphasizes the fact that the best way to individualize clozapine doses is to base them on blood levels. Doing so has the added advantages of lessening side effects and allowing adherence to be monitored. However, facilities for blood levels are not always available. Standardized dosing schedules could be used in such instances[132].

Many of the side effects encountered with clozapine are dose-dependent including sedation, tachycardia, hypersalivation, enuresis, constipation, delirium, obsessive-compulsive symptoms, seizures, and orthostatic hypotension[81,120,138] Among all antipsychotics, the prevalence of metabolic dysfunction or metabolic syndrome is the highest for clozapine and olanzapine[81,126,127,132,139]. Whether metabolic side effects are also dose-dependent is not clear[81,138]. However, systematic reviews and meta-analyses have indicated a dose-outcome association between clozapine and metabolic side effects, particularly with lipid levels and weight gain[140,141]. Risk factors for metabolic syndrome include higher baseline weight or body mass index, gender, non-White, possibly Asian ethnicity, and several genetic and peptide markers [126,127,136,139,142]. Somewhat paradoxically, metabolic disturbances are also associated with a reduction in symptoms[126,127].

Table 8 Steps for ensuring optimal clozapine treatment[65,81,110,111,120,123,132]

Steps for ensuring optimal clozapine treatment	
Adequate assessment	Diagnosis should be established properly. Comorbid conditions should be looked for. Adherence should be determined. Symptoms and other outcome domains should be preferably rated using validated instruments. Caregiver burden and coping should be assessed. Stressors and adverse circumstances should be evaluated.
Proper dosing	Inter-individual and ethnic variability in optimal doses should be considered. If facilities for serum levels are available, doses should be titrated to ensure plasma levels > 350 ng/mL. Doses should be increased slowly with careful monitoring of side effects to reduce the burden of dose-dependent side effects.
Adequate duration	A minimum of 2-3 mo is considered necessary. Durations could be shorter in those with high risk of aggression or self-harm. Durations could be longer in those with negative or cognitive symptoms and in partial responders.
Managing side effects	Many of the common side effects of clozapine can be managed by slow titration, using the least effective dose, reducing doses when side effects develop, adding medications, or adopting lifestyle changes to counter side effects. Additionally, careful monitoring should be carried out for the more serious and idiosyncratic adverse reactions such as agranulocytosis and cardiopulmonary complications.
Managing non-adherence	Careful monitoring of adherence based on multiple sources is necessary. Managing side effects, educating patients to deal with negative attitudes to clozapine, developing a trusting alliance to improve motivation, caregiver education and support to increase their involvement in the patient's care may help. These measures should ideally be initiated right at the beginning of treatment. Use of long-acting antipsychotic injections may be considered.
Collaboration with patients and caregivers	Both patients and caregivers should be the focus of treatment. Measures should be tailored according to their needs. Goals of treatment should be reduction of symptoms and distress, improving support, forging effective alliances, and promoting patient and caregiver engagement. Simple psychosocial measures including cognitive or behavioural strategies, psychoeducation, and emotional and practical support should be implemented at the start of treatment or as early as possible. More structured interventions can be tried depending on availability of resources and expertise.
Addressing clinician related barriers	Clinicians' lack of awareness and experience of clozapine treatment and negative attitudes towards clozapine use should be addressed by proper education, dissemination of information, and dedicated facilities.

Optimizing clozapine doses is the principal way of managing most dose-dependent side effects. Using the lowest effective dose, slow increase in doses, and dose adjustments to minimize side effects is always recommended[81,120,123]. Discontinuation of concomitant medications that might not be essential also reduces the side effect burden[120]. Only serious and life-threatening adverse reactions such as agranulocytosis and some cardiopulmonary complications require abrupt discontinuation of clozapine[81,120]. Some side effects such as neuroleptic malignant syndrome, thromboembolism, or diabetic ketoacidosis may require temporary discontinuation followed by re-initiation of clozapine[81]. In most other situations, the dose of clozapine should be reduced very gradually to avoid worsening of clinical state or emergence of withdrawal symptoms[120]. When side effects persist despite optimizing the dose of clozapine, the options include adding other medications, instituting non-pharmacological measures to manage side effects, or combining clozapine with another antipsychotic[120,138]. In the case of metabolic syndrome, adequate treatment of risk factors and metabolic derangements is essential[143].

Meta-analyses of interventions for metabolic side effects have shown that adjunctive metformin is the most effective strategy[144,145]. Behavioural weight management strategies are also recommended though the evidence for their efficacy is uncertain [120,138,144]. Adding aripiprazole to clozapine to reduce both the clozapine dose and metabolic disturbances has also been suggested, but the evidence for this option is limited[120,144].

Minimizing the side effect burden is necessary because about 40% of the patients (range 21%-67%) stop taking clozapine in the first few years of treatment[82,84,86,87,146]. In 20%-30% of them, discontinuation is because of intolerable side effects, though intentional non-adherence appears to be somewhat more common[84,85,87,88,147]. Managing non-adherence requires open and non-judgmental discussions about medication-taking with patients, monitoring of adherence based on all available methods including caregiver reports, education to deal with misconceptions about treatment, and building trusting alliances with patients and families to ensure continued treatment. A collaboration with the patient and the family is an essential part of optimizing clozapine treatment that is often overlooked[65,110,111,120]. Shared decision-making about treatment, education, stress-management, support, and involvement of caregivers are ways of ensuring truly collaborative alliances.

Lastly, increasing evidence indicates substantial underutilization and delayed use of clozapine[148,149]. Clinician's lack of awareness and experience with clozapine, their misplaced concerns about its use, and the discrepancy between clinicians' and patients' attitudes regarding clozapine are among the main causes of inappropriate use

of clozapine[150,151]. Therefore, dealing with these clinician-related barriers is also necessary to ensure the proper use of clozapine.

CONCLUSION

Clozapine resistance is probably one of the most difficult conditions that clinicians treating patients with schizophrenia are likely to encounter. Unfortunately, the existing research evidence does not provide any firm guidelines about treatment options once clozapine fails. However, because of the seriousness of the condition and the widespread negative impact of CRS, clinicians need to look beyond the evidence and rely on consensus-based recommendations. At present, effective ways to deal with CRS are to optimize clozapine treatment, choose among the best available options judiciously, explore newer ways of augmentation, and adopt a holistic approach to treatment that includes simple psychosocial measures in addition to pharmacological ones. Finally, cautious optimism, commitment to treatment, patience, and persistence from clinicians, patients, and caregivers are almost always required for the effective use of clozapine.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 August 19; 11(8): 449-462

DOI: 10.5498/wjp.v11.i8.449

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

Impact of spiritual care on the spiritual and mental health and quality of life of patients with advanced cancer

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Author contributions: Sun XH contributed to study design, experimental studies, data analysis, and manuscript writing; Liu X contributed to literature research, experimental studies, data analysis, and statistical analysis; Zhang B contributed to literature research, data analysis, and statistical analysis; Wang YM contributed to experimental studies and data acquisition; Fan L contributed to study design, manuscript revision, and manuscript final version approval.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Shengjing Hospital of China Medical University (Approval No.: 2018PS362K).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors have no conflict of interest

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Abstract

BACKGROUND

Cancer is a growing threat to human health. Due to the double torment of cancer and cancer treatment, patients with advanced cancer generally have a low quality of life. At present, there is a lack of systematic spiritual care plans for patients with advanced cancer as well as systematic guidance plans on the specific clinical application of spiritual care for advanced cancer patients. We hypothesized that our care plan would be effective in improving the spiritual and mental health and quality of life of patients with advanced cancer.

AIM

To construct a spiritual care plan suitable for Chinese patients with advanced cancer through literature analysis.

METHODS

From February to December 2018, through purpose sampling, we selected 100 advanced cancer patients from the Oncology Department and Hospice Ward of a tertiary hospital in Liaoning Province who met the study standards. Patients were randomly divided into experimental and control groups, with 50 cases in each

group. The control group received the current routine care, while the experimental group received the advanced cancer spiritual care intervention in addition to routine care.

RESULTS

After the intervention, the overall spiritual health score for the experimental group was higher than that of the control group (4.68 ± 1.36 *vs* 3.63 ± 1.71). The difference between the groups was statistically significant ($P < 0.05$). The proportion of anxiety-free patients in the experimental group was 95.45%, which was significantly higher than the 60.98% in the control group. Moreover, the proportion of non-depressed patients in the experimental group was 97.73%, which was significantly higher than the 85.37% in the control group ($P < 0.05$). The overall quality of life score for the experimental group was significantly higher than that of the control group (5.36 ± 1.16 *vs* 4.39 ± 1.36, $P < 0.05$).

CONCLUSION

Our spiritual care plan for patients with advanced cancer could improve their spiritual health and quality of life and reduce negative mental health symptoms.

Key Words: Cancer; Spiritual care; Depression; Anxiety; Spiritual health; Quality of life

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Core Tip: We constructed a spiritual care program for advanced cancer patients suitable for Chinese culture and national conditions, and carried it out for advanced cancer patients. Results showed that the spiritual health status and quality of life of advanced cancer patients were improved, and their anxiety and depression reduced.

Citation: Sun XH, Liu X, Zhang B, Wang YM, Fan L. Impact of spiritual care on the spiritual and mental health and quality of life of patients with advanced cancer. *World J Psychiatr* 2021; 11(8): 449-462
URL: https://www.wjgnet.com/2220-3206/full/v11/i8/449.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i8.449

INTRODUCTION

As the environment is deteriorating, human health is facing a growing number of threats. One such threat that has grown increasingly significant is cancer. It has been estimated that the number of cancer patients worldwide had risen to 3 million in 2020, two-thirds of which are advanced cancers with low chances of cure[1]. Patients with advanced cancer generally have a low quality of life. Due to the double torment of cancer and cancer treatment, their psychological, physical, social, familial, and other aspects of their lives are all negatively affected in varying degrees[2]. Spiritual care is a complex and multidimensional concept with different definitions[3] and refers to patients seeking the meaning of life, gaining peace and comfort, obtaining emotional support from family members, and alleviating the fear of death during illness with the help of professional medical service teams, social groups, families, volunteers, and religious personnel, thereby improving the quality of life of patients with advanced cancer[4]. Global research on the spiritual care of patients with advanced cancer is relatively novel. A relatively mature care model that includes a professional care team and complete tools for evaluating the spiritual needs of patients with advanced cancer has been created. At present, the spiritual care model in China is based on the four-in-one holistic care model of body-mind-community-spirit. Intervention measures are embodied in several aspects, such as peaceful, holistic, special, hospice, overall nursing care, palliative treatment, death education, *etc*. However, there is a lack of systematic spiritual care plans for patients with advanced cancer as well as a lack of systematic guidance plans on the specific clinical application of spiritual care for them, which greatly reduces the effectiveness of care. The purpose of spiritual care is to pay attention to the patient's attitude towards the disease. This means that the patient's

to declare.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Manuscript source: Unsolicited manuscript

Specialty type: Nursing

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 18, 2021
Peer-review started: March 18, 2021
First decision: June 5, 2021
Revised: June 18, 2021
Accepted: July 14, 2021
Article in press: July 14, 2021
Published online: August 19, 2021

P-Reviewer: Kay TM, Wittkopf N
S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Wang LYT

spiritual care is more important than their physical care[5]. We used advanced global spiritual care guidelines as references and combined them with information around the Chinese setting to construct a spiritual care plan that was suitable for Chinese culture. Our care plan achieved good results when applied to advanced cancer patients.

MATERIALS AND METHODS

Construction of a spiritual care plan for patients with advanced cancer

We searched the Chinese Biological Medicine Database, China National Knowledge Infrastructure, Wanfang Database, and VIP Information Resource System using Chinese search terms such as cancer, tumor, advanced stage, spirituality, spiritual care, spiritual intervention, *etc.* We also searched the PubMed, Science Citation Index Expanded, and Web of Science databases. To collect data as comprehensively as possible, we combined the aforementioned keywords in Chinese and English and included references from the retrieved literature. We invited nine experts in oncology and its related fields to revise the constructed spiritual care plan for advanced cancer patients through meetings with experts[6]. The selection criteria for the experts were as follows: (1) working in the fields of advanced cancer clinical nursing, nursing management, nursing education, advanced cancer clinical medicine, psychology, and other related disciplines; (2) having an under graduate degree or higher; (3) having a medium-grade professional title or higher; (4) having 10 or more years of work experience in their professional fields and being familiar with the content of our study; and (5) participating in our study voluntarily.

Evaluative research on the spiritual care plan for patients with advanced cancer

From February to December 2018, cancer patients from the Oncology Department and Hospice Ward of a tertiary hospital in Liaoning Province who qualified for our study were selected through objective sampling. Patients were stratified according to the different departments to which they were admitted. In each ward, 20% of the actual number of hospitalizations were sampled. We sampled a total of 100 patients and used randomized grouping to separate them into our study groups. The inclusion criteria were as follows: (1) a histological or cytological diagnosis of a tumor node metastasis stage III or IV malignant tumor; (2) age >18 years; (3) being able to communicate and understand; (4) being able to provide informed consent and participate voluntarily; and (5) being aware of their condition. The exclusion criteria were as follows: (1) impaired consciousness; and (2) being unable to understand or fill in the scale correctly.

Research tools

General information survey form: This included details of the patient's age, gender, education, family income, medical expense payments, *etc.*

Clinical data questionnaire: This questionnaire was self-designed and based on the literature review. It included information such as the patient's cancer diagnosis and stage, as well as whether there was metastasis.

The Chinese version of the European Organization for Cancer Research and Treatment Quality of Life Questionnaire-Spiritual Well-Being 32 (EORTC QLQ-SWB32)[7] scale: The original English scale was developed and validated by the EORTC QOL Group in 2017 for the assessment of the spiritual health status of patients with advanced cancer. EORTC QLQ-SWB32 consists of 32 items, with 22 items forming four multiitem scales: Existential; Relationship with Self; Relationships with Others; and Relationship with Someone or Something Greater. The first 31 items were scored using a four-point Likert Scale with answers ranging from "not at all" to "very". Item 32 was mainly used to reflect the patient's overall spiritual health status: 0 point, did not know or was unable to answer; 1 point, very poor; 7 points, very good. As the score increased, the patient's overall spiritual health improved[8]. In 2017, the author translated the scale into Chinese version[9] (it is not an official EORTC translation), and the total Cronbach α coefficient of the scale was 0.808.

The General Hospital Anxiety and Depression Scale: This scale was created by Zigmond *et al*[10] in 1983 and translated into Chinese by Ye *et al*[11] in 1993 to form its Chinese version. It is used in general hospitals to assess patients' anxiety and depression. Cronbach's α for the Chinese version of the scale was 0.870.

The Chinese version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative (EORTC QLQ-C15-PAL): The EORTC QLQ-C15-PAL was based on the EORTC QLQ-C30 and created by Groenvold *et al*[12] in 2005. It was translated into Chinese by Luo *et al*[13] in 2014 and was used to assess the quality of life of cancer patients in palliative care. Excluding the emotional function dimension, Cronbach's α values for the other dimensions were all > 0.7.

Research content

Intervention plan for the control group: The control group received routine care plans, including general and symptomatic care; tumor chemotherapy, radiotherapy, biotherapy, intracavitary therapy care, and psychological care.

Intervention plan for the experimental group: Based on routine care implementation and guided by the "Spiritual Care Plan for Patients with Advanced Cancer", we provided spiritual care for patients with advanced cancer. This included the following services: (1) Admission evaluation: For the patients who met the inclusion criteria, after informed consent was obtained from the patient and their caregivers, the research participant's basic information was collected and their spiritual care needs and spiritual health status were evaluated; (2) Spiritual care intervention: From 2–3 d after admission, based on the "Spiritual Care Plan for Advanced Cancer Patients" that we created, the researchers and oncology specialist nurses from each department worked together to carry out the intervention. Interventions included participating in activities and watching face-to-face guidance videos or targeted explanations and were implemented in a small conference room or ward in the Oncology Department. Patients' examination, treatment, nursing, and meal times were avoided, and their free and rest times were designated as the times when the interventions could take place; this was usually between 3:00 pm and 5:00 pm. A total of five interventions were carried out, each 30–60 min long. The patients' psychological and emotional states were closely monitored during each intervention. If the patient felt unwell, they could choose to take a break or have their session at another time; and (3) Post-intervention evaluation: After the intervention, patients' self-expression was asked in time. They were also asked to fill in the spiritual health assessment scale and other questionnaires to analyze quantitatively the effects of the spiritual care plan on patients with advanced cancer.

Data collection and analysis

The researchers collected data before and after the intervention. Before collection, our study's purpose, requirements, and precautions were explained, and patients were reassured of the confidentiality of the questionnaire and their data. After the patients' consent was obtained, they were asked to fill in a questionnaire to ensure objectivity. EpiData 3.1 was used for data entry, and the database was established using the Chinese version of SPSS version 21 (SPSS Inc., IBM Corp., Armonk, NY, United States). General data were depicted using statistics: Count data were expressed using the rate and composition ratio; and measurement data were expressed using the mean ± SD and comparison using a *t*-test and non-parametric test. Frequency, percentage, and the χ^2 square test was used for count data. A P value < 0.05 was considered statistically significant.

RESULTS

Construction of a spiritual health care intervention plan for patients with advanced cancer

A total of 10 articles that met the requirements were included and analyzed in our study. Nine experts in oncology and its related fields were invited to revise the constructed spiritual care plan for patients with advanced cancer. Finally, a final version of the spiritual health care intervention plan was developed.

Evaluation of the effect of application of the spiritual health care intervention plan for patients with advanced cancer

The effective sample sizes for the experimental and control groups were 41 and 44 cases, respectively, and the final effective sample size was 85 cases. The age range for

the experimental group was 28–83-years-old (50.05 ± 12.44-years-old), and for the control group it was 27–79-years-old (54.88 ± 13.78-years-old). The independent sample *t*-test results showed that there was no significant difference in age when the two groups were compared (t = 0.059, P = 0.953). The general demographic characteristics of the two groups were count data, such as gender, ethnicity, living conditions, religious beliefs/cultural beliefs, highest education, *etc.* Pearson's χ^2 test was used for the comparison, and the differences were not statistically significant (P > 0.05). The general data of the two groups were comparable (Table 1).

Clinical data

The differences in the research participants' clinical data were not statistically significant (P > 0.05), indicating two groups were comparable (Table 2).

Spiritual health

Before the spiritual care intervention, there was no significant difference in the spiritual health scores between the two groups (P > 0.05). The spiritual health scores of the two groups were comparable (Table 3).

After the spiritual care intervention, there were no significant differences in the existence (EX) and relationship with self (RS) scores when the two groups were compared (P > 0.05); thus, spiritual care was not yet considered meaningful to the patients' EXs and RSs. However, the differences in the relationship with others (RO), relationship with something greater (RSG), and overall spiritual health scores were statistically significant (P < 0.05 for all; Table 4).

Anxiety and depression

When the anxiety levels from the two groups before and after the spiritual care intervention were compared, the difference in anxiety levels before the intervention was not statistically significant (P > 0.05), indicating the anxiety levels of the two groups were comparable. After the intervention, the difference in anxiety levels when the groups were compared was statistically significant (P < 0.05; Table 5).

The comparison of the two groups' depression before and after the spiritual care intervention showed that there was no statistically significant difference in depression between the groups before the intervention (P > 0.05), indicating the depression levels of the two groups were comparable. The difference in the levels of depression after the intervention when the groups were compared was statistically significant (P < 0.05; Table 6).

Quality of life

The Chinese version of the EORTC QLQ-C15-PAL was used to evaluate the quality of life of the two groups before the intervention. The differences in the results were not statistically significant (P > 0.05), and the data from the two groups were comparable (Table 7).

After the spiritual care intervention, there was no statistically significant difference in the quality of life when the patient groups were compared in terms of physical function, pain, dyspnea, insomnia, and constipation (P > 0.05). Thus, spiritual care was not yet considered meaningful with regard to these parameters. The differences between the groups in terms of symptoms such as emotional function, fatigue, nausea and vomiting, loss of appetite, and overall quality of life were statistically significant (P < 0.05; Table 8).

DISCUSSION

Construction of an intervention plan for the spiritual healthcare of patients with advanced cancer

In this study, the first draft of the spiritual care plan for patients with advanced cancer was formulated through literature analysis. Some items of the plan were deleted, revised, or adjusted through expert meetings. When the experts were selected, their representativeness was fully considered. The literature analysis combined with the expert meeting made the spiritual care plan practical and scientific.

General characteristics and the baseline level of the participants

Studies have demonstrated that the general demographic characteristics and clinical data of patients with advanced cancer (such as age, gender, race, tumor type, cancer

Table 1 General information characteristics, *n* (%)

Characteristics	Control group (*n* = 41)	Experimental group (*n* = 44)	χ^2	*P* value
Gender			0.286	0.593
Male	10 (24.4)	13 (29.5)		
Female	31 (75.6)	31 (70.5)		
Ethnicity			4.027	0.259
Han	34 (82.9)	42 (95.5)		
Manchu	5 (12.2)	2 (4.5)		
Hui	1 (2.4)	0 (0.0)		
Mongolian	1 (2.4)	0 (0.0)		
Marital status			1.777	0.777
Single	2 (4.9)	3 (6.8)		
Married	36 (87.8)	35 (79.5)		
Cohabitation	0 (0.0)	1 (2.3)		
Divorced	1 (2.4)	1 (2.3)		
Widowed	2 (4.9)	4 (9.1)		
Religious beliefs			1.623	0.805
Nil	32 (78.0)	34 (77.3)		
Christian	2 (4.9)	4 (9.1)		
Buddhist	5 (12.2)	5 (11.4)		
Taoist	1 (2.4)	0 (0.0)		
Muslim	1 (2.4)	1 (2.3)		
Cultural beliefs			7.459	0.059
Nil	21 (51.2)	23 (52.3)		
Chinese traditional culture	13 (31.7)	5 (11.4)		
Marxist-Leninist, Maoist, Deng, and the "Three Represents"	7 (17.1)	15 (34.1)		
Others	0 (0.0)	1 (2.3)		
Highest education			3.734	0.443
Primary school	9 (22.0)	6 (13.6)		
Junior high school	10 (24.4)	18 (40.9)		
High school	13 (31.7)	9 (20.5)		
University	8 (19.5)	10 (22.7)		
Postgraduate and above	1 (2.4)	1 (2.3)		
Working status			4.635	0.327
Retirement	20 (48.8)	24 (54.5)		
Unemployed	10 (24.4)	4 (9.1)		
Part time	0 (0.0)	1 (2.3)		
Full time	3 (7.3)	3 (6.8)		
On sick leave	8 (19.5)	12 (27.3)		
Profession			3.994	0.262
Worker	14 (34.1)	12 (27.3)		
Farmer	9 (22.0)	6 (13.6)		
Staff	6 (14.6)	4 (9.1)		

Other	12 (29.3)	22 (50.0)		
Monthly household income (in CNY)			–0.436[1]	0.663
≤ 1000	10 (24.4)	10 (22.7)		
1000–2999	17 (41.5)	15 (34.1)		
3000–4999	8 (19.5)	13 (29.5)		
5000–6999	1 (2.4)	4 (9.1)		
≥ 7000	5 (12.2)	2 (4.5)		
Payment method for medical expenses			5.857	0.320
Social medical insurance	28 (68.3)	37 (84.1)		
Rural cooperative medical service	9 (22.0)	4 (9.1)		
Free medical care	2 (4.9)	0 (0.0)		
Commercial medical insurance	1 (2.4)	1 (2.3)		
Self-paid medical care	1 (2.4)	1 (2.3)		
Others	1 (2.4)	1 (2.3)		
Primary caregivers			7.971	0.240
Unattended	1 (2.4)	4 (9.1)		
Parents	3 (7.3)	6 (13.6)		
Child	11 (26.8)	11 (25.0)		
Spouse	24 (58.5)	16 (36.4)		
Relative	2 (4.9)	4 (9.1)		
Nurses/nannies	0 (0.0)	2 (4.5)		
Others	0 (0.0)	1 (2.3)		

[1]The Mann-Whitney *U* test.

location, employment status, religious beliefs, *etc.*) have an impact on their spiritual health[14-16]. The older the patient, the better their spiritual health. This holds particularly true for those older than 60 years, who have been shown to have significantly better spiritual health[9,17]. Women demonstrate better spiritual health than men; however, the aspects of spiritual health (belief, peace, meaning, overall spiritual health) are not balanced. The level of spiritual health also differs among patients with advanced cancer belonging to different races. However, some studies have demonstrated that spiritual health has nothing to do with general characteristics such as age, gender, race, cancer grade, metastasis, medical insurance, marital status, religious beliefs, *etc.*[18]. The inconsistency of conclusions may be related to different sample size or data collection methods. The general demographic data of the two groups in our study were consistent, except for their living conditions. Consistency was also demonstrated between the two groups in all aspects of the clinical data. Thus, the baseline levels of the two groups were guaranteed before the intervention.

Spiritual care improving spiritual health of patients with advanced cancer

In our study, we found that the provision of spiritual care to patients with advanced cancer could significantly improve their overall spiritual health. The overall spiritual score of the experimental group was higher than that of the control group (4.68 ± 1.36 *vs* 3.63 ± 1.71), and the difference between the two groups was statistically significant ($P = 0.002$). This finding was consistent with the results from other studies that found that spiritual care could promote the spiritual health of patients with advanced cancer [19-22]. In our study, after spiritual intervention, there were inconsistencies in the findings regarding the four dimensions of spiritual health when the two groups were compared. The RO and RSG scores for the experimental group were higher than those for the control group (3.07 ± 0.57 *vs* 2.81 ± 0.58 and 2.65 ± 0.40 *vs* 2.18 ± 0.42, respectively). The differences between the RO and RSG scores before and after the intervention were statistically significant ($P < 0.05$). However, the findings regarding

Table 2 Patients' clinical data, *n* (%)

	Control group	Experimental group	χ^2/Z score	*P* value
Cancer diagnosis			4.693	0.584
Breast cancer	6 (14.60)	4 (9.10)		
Lung cancer	7 (17.10)	6 (13.60)		
Gastrointestinal cancer	7 (17.10)	12 (27.30)		
Nasopharyngeal cancer	2 (4.90)	4 (9.10)		
Gynecological cancer	14 (34.10)	16 (36.40)		
Pancreatic cancer	2 (4.90)	0 (0.00)		
Others	3 (7.30)	2 (4.50)		
Metastasis			0.848	0.357
Yes	16 (39.00)	13 (29.50)		
No	25 (61.00)	31 (70.50)		
Clinical manifestation status			-0.028[1]	0.978
Grade 0	16 (40.00)	9 (20.50)		
Grade 1	7 (17.50)	23 (52.30)		
Grade 2	9 (22.50)	7 (15.90)		
Grade 3	4 (10.00)	5 (11.40)		
Grade 4	4 (10.00)	0 (0.00)		
Stratification			5.320	0.150
Asymptomatic, stable, anti-cancer	6 (15.40)	5 (11.40)		
Asymptomatic, stable, not anti-cancer	2 (5.10)	1 (2.30)		
Symptomatic, anti-cancer remission	24 (61.50)	36 (81.80)		
Symptomatic, symptom control	7 (17.90)	2 (4.50)		
Treatment			16.467	0.110
Palliative care	7 (17.10)	0 (0.00)		
Radiotherapy	0 (0.00)	5 (11.40)		
Chemotherapy	28 (68.30)	31 (70.50)		
Hormone Therapy	0 (0.00)	2 (4.50)		
Chemoradiotherapy	6 (14.60)	4 (9.10)		
Others	0 (0.00)	2 (4.60)		

[1]The Mann-Whitney *U* test.

the EX and RS scores were not statistically significant. This may have been related to the characteristics of the different dimensions of spiritual health. The purpose of spiritual care is to help patients seek the meaning of life, self-realization, hope and creation, faith and trust, peace and comfort, prayer, love and forgiveness, *etc.*, while suffering from illness and pain[23]. Therefore, as core components of quality oncology, spiritual health and spiritual care both promote and influence each other[24].

Spiritual care reducing the levels of anxiety and depression in advanced cancer patients

In our study, after the spiritual care intervention, the number of advanced cancer patients that did not feel anxious and depressed increased significantly, and the differences in these values were statistically significant ($P < 0.001$). This was consistent with the results from a study by Chida *et al*[25], as well as those from other studies, which demonstrated that in advanced cancer patients, effective spiritual care can

Table 3 Spiritual health scores before spiritual care intervention

Dimension	Control group (*n* = 41)	Experimental group (*n* = 44)	*t*/*Z* score	*P* value
EX	2.59 ± 0.69	2.75 ± 0.74	0.986	0.324
RS	2.37 ± 0.59	2.24 ± 0.58	0.983	0.328
RO	2.86 ± 0.59	2.78 ± 0.62	0.593	0.554
RSG	2.55 ± 0.32	2.57 ± 0.43	0.208	0.836
Overall spirituality	2.59 ± 0.69	2.75 ± 0.74	-1.439[1]	0.150

[1]The Mann-Whitney *U* test. EX: Existence; RS: Relationship with self; RO: Relationship with others; RSG: Relationship with something greater.

Table 4 Spiritual health scores after spiritual care intervention

Dimension	Control group (*n* = 41)	Experimental group (*n* = 44)	*t*/*Z* score	*P* value
EX	2.51 ± 0.68	2.79 ± 0.75	–1.811	0.074
RS	2.39 ± 0.59	2.40 ± 0.53	–0.043	0.966
RO	2.81 ± 0.58	3.07 ± 0.57	–2.075	0.041[a]
RSG	2.18 ± 0.42	2.65 ± 0.40	–4.634[1]	*P* < 0.001
Overall spirituality	3.63 ± 1.71	4.68 ± 1.36	-3.077[1]	0.002[a]

[a]*P* < 0.05. EX: Existence; RS: Relationship with self; RO: Relationship with others; RSG: Relationship with something greater.
[1]The Mann-Whitney *U* test.

Table 5 Anxiety status before and after spiritual care intervention, *n* (%)

	Control group	Experimental group	*Z* score	*P* value
Before intervention			-0.558	0.577
No anxiety	22 (53.66)	25 (56.82)		
Critical anxiety	10 (24.39)	13 (29.55)		
Obviously anxious	9 (21.95)	6 (13.64)		
After intervention			-7.834	*P* < 0.001
No anxiety	25 (60.98)	42 (95.45)		
Critical anxiety	8 (19.51)	2 (4.55)		
Obviously anxious	8 (19.51)	0 (0.00)		

reduce negative emotions such as anxiety and depression, reduce suicide risk, and improve their mental health[25,26]. The higher the level of spiritual health, the higher the quality of life; thus, the happier the patient is, the less depressed, anxious, and fatigued they feel, and the less pain they experience[18]. Spiritual health is a valuable coping mechanism. It has unique advantages in its ability to protect cancer survivors from depressive symptoms[27]. As a part of overall health, spiritual health plays an important role in coping with disease-related psychological symptoms and influencing medical decisions before death[28]. Spiritual care interventions can quickly, accurately, and reliably identify the spiritual health of patients with advanced cancer and help them understand their own life, feelings, hope, peace, and other mental states. In our study, following the spiritual care intervention, we found that the emotional function score of the experimental group was lower than that of the control group (2.98 ± 1.34 *vs* 3.73 ± 1.72). This was consistent with the results from the patients' anxiety and depression investigations that were performed after the spiritual intervention.

Table 6 Depression before and after spiritual care intervention, *n* (%)

	Control group	Experimental group	Z score	*P* value
Before intervention				
No depression	22 (53.66)	26 (59.09)	–0.714	0.475
Critical depression	9 (21.95)	11 (25.00)		
Obvious depression	10 (24.39)	6 (13.64)		
After intervention				
No depression	35 (85.37)	43 (97.73)	–2.068	0.039[a]
Critical depression	5 (12.20)	1 (2.27)		
Obvious depression	1 (2.44)	0 (0.00)		
No depression	22 (53.66)	26 (59.09)	–0.714	0.475

[a]$P < 0.05$.

Table 7 Quality of life before spiritual care intervention

Dimension	Control group (*n* = 41)	Experimental group (*n* = 44)	Z score	*P* value
Function				
Physical function	5.90 ± 2.58	5.52 ± 1.72	–0.040	0.968
Emotional function	4.10 ± 1.79	3.80 ± 1.77	–0.915	0.360
Symptom				
Fatigue	4.63 ± 1.95	4.61 ± 1.77	–0.018	0.986
Nausea and vomiting	2.05 ± 1.02	1.80 ± 0.98	–1.187	0.235
Pain	3.56 ± 1.63	3.55 ± 1.73	–0.155	0.877
Dyspnea	1.27 ± 0.55	1.41 ± 0.69	–0.895	0.371
Insomnia	1.90 ± 1.09	2.02 ± 0.90	–0.958	0.338
Poor appetite	2.10 ± 0.97	1.84 ± 0.94	–1.306	0.191
Constipation	1.88 ± 0.98	1.82 ± 1.02	–0.450	0.653
Overall quality of life	4.24 ± 1.50	4.55 ± 1.50	-0.822	0.411

Spiritual care improving the quality of life of patients with advanced cancer

In our study, after the spiritual intervention, we found that the overall quality of life score of the experimental group was higher than that of the control group (5.36 ± 1.16 *vs* 4.39 ± 1.36), and that the difference between the two groups was statistically significant ($P = 0.002$). This was consistent with the results from several studies[29-31]. Spiritual health, as a potential or direct influencing factor, can effectively improve the quality of life of patients with advanced cancer. It can also improve the efficacy of palliative care and is an important indicator for evaluating the quality of life of patients with advanced cancer[32]. In terms of fatigue, the fatigue score of the experimental group was lower than that of the control group (3.41 ± 1.26 *vs* 4.39 ± 1.64), and this difference was statistically significant ($P = 0.005$). We found that spiritual care can alleviate the fatigue experienced by cancer patients, which was consistent with the results from studies by Rabow *et al*[18] and Heidari *et al*[33]. All cancer patients experience fatigue, and higher fatigue scores are observed in patients with stage IV tumors. There is a significant negative correlation between fatigue scores and spiritual health. The more obvious the symptoms of fatigue and the more severe the fatigue that the cancer patient is experiencing, the worse their spiritual health is. Therefore, we propose that fatigue can be used as the primary negative predictor of the spiritual health in patients with advanced cancer[13].

Table 8 Quality of life after spiritual care intervention

Dimension	Control group (*n* = 41)	Experimental group (*n* = 44)	*Z* score	*P* value
Function				
Physical function	5.68 ± 2.61	4.70 ± 1.65	–1.590	0.112
Emotional function	3.73 ± 1.72	2.98 ± 1.34	–2.103	0.035[a]
Symptom				
Fatigue	4.39 ± 1.64	3.41 ± 1.26	–2.829	0.005[a]
Nausea and vomiting	2.05 ± 1.00	1.52 ± 0.73	–2.521	0.012[a]
Pain	3.56 ± 1.45	2.95 ± 1.06	–1.857	0.063
Dyspnea	1.51 ± 0.67	1.36 ± 0.65	–1.198	0.231
Insomnia	1.83 ± 1.05	1.66 ± 0.68	–0.196	0.844
Poor appetite	2.07 ± 0.93	1.66 ± 0.78	–2.179	0.029[a]
Constipation	1.83 ± 0.89	1.50 ± 0.73	–1.823	0.068
Overall quality of life	4.39 ± 1.36	5.36 ± 1.16	-3.077	0.002[a]

[a]$P < 0.05$.

In our study, the effect of spiritual care on pain was not obvious, and the difference between the findings from the two groups was not statistically significant ($P = 0.063$). However, this finding was inconsistent with the results from other studies[34]. This may have been related to the short duration of the intervention or the different grades of pain. Many studies have confirmed that patients with advanced cancer experience significant problems with pain, and the severity of the pain has a negative correlation with their spiritual health[35]. The more severe the patient's pain, the worse their spiritual health is. Our study also found that after the spiritual care intervention, the nausea and vomiting and loss of appetite scores for the experimental group were lower than those for the control group (1.52 ± 0.73 *vs* 2.05 ± 1.00 and 1.66 ± 0.78 *vs* 2.07 ± 0.93, respectively) and these differences were statistically significant. This may have been due to the patients' calmness after undergoing spiritual care. Their psychological disposition had an impact on their physiological function, thus reducing their gastrointestinal reaction and increasing their appetite.

CONCLUSION

Although spiritual care in China began relatively late, many studies have verified that when it was applied to the clinical care of patients with advanced cancer, it could effectively guide clinical nurses or palliative care teams towards providing nursing services to patients with advanced cancer in a systematic, scientific, and targeted manner. We included specific spiritual care content for cancer patients based on psychological cancer care, providing specific help and guidance strategies for the spiritual care of patients with advanced cancer, and complementing psychological care to promote the quality of life of this patient population. We made the palliative care team and its supporters more aware of the spiritual confusion that patients with advanced cancer experience, guided the team to conduct comprehensive patient assessments, implemented spiritual care for the spiritual problems that patients with advanced cancer encountered, and evaluated the effects of this intervention both before and after its implementation. In addition, this intervention can draw the attention of medical staff to the spiritual health of patients with advanced cancer and strengthen their attention to spiritual care. Although it cannot extend the length of the patient's lifespan, it can allow the patient to complete their last journey of life quietly, peacefully, and without regrets.

ARTICLE HIGHLIGHTS

Research background

The quality of life of patients with advanced cancer is generally low, including psychological, physical, social, family, and other aspects. Spiritual care is thought to improve the quality of life for people with advanced cancer. While developed countries have developed mature care models, there is currently a lack of systematic spiritual care programs for patients with advanced cancer in developing countries. This study referred to the mature spiritual care programs in developed countries, and combined the national conditions of China to construct spiritual care programs suitable for Chinese culture and evaluated its effects.

Research motivation

This study constructed a spiritual care plan suitable for Chinese culture and provided a basis for clinicians to take intervention measures to improve the spiritual health of patients with advanced cancer.

Research objectives

This study aimed to build a spiritual care program for advanced cancer patients suitable for China's national conditions and evaluated its application effect in the Chinese population. Future research could explore the extensibility of this program in different cancer populations.

Research methods

This research adopted the Delphi method to construct the spiritual care plan and the method to study the randomly assigned experimental group and control group. The experimental group used the spiritual care plan, while the control group used conventional care plan. The two groups of patients' were evaluated for spiritual health score, anxiety score, depression score and quality of life score to evaluate the effect of spiritual care plan.

Research results

The results showed that the spiritual-care group had higher overall spiritual health scores, lower prevalence of anxiety and depression, and higher overall quality of life scores than the control group, indicating that the spiritual care plan was an effective solution for Chinese patients with advanced cancer.

Research conclusions

The spiritual care program for patients with advanced cancer developed in this study could improve the spiritual health and quality of life of patients with advanced cancer and reduce negative emotions such as anxiety and depression. Spiritual care for patients with advanced cancer is recommended in oncology and hospice units.

Research perspectives

Future studies may evaluate the generalizability of the plan in a broader population of cancer patients.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 August 19; 11(8): 463-476

DOI: 10.5498/wjp.v11.i8.463

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Therapeutic use of melatonin in schizophrenia: A systematic review

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Author contributions: Duan C and Castle D designed the research; Duan C performed the search; Duan C and Jenkins ZM extracted the data and wrote the paper; Castle D supervised the paper; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Sleep dysfunction is a common problem in people with schizophrenia, and side effects of treatment often exacerbate metabolic and cardiovascular risk and may induce extrapyramidal side effects. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenously produced hormone which has demonstrated direct and indirect antioxidant and neuroprotective effects. Previous studies have explored the use of exogenous melatonin in improving sleep outcomes in the general population, yet indications for use in schizophrenia are unclear.

AIM

To synthesize the evidence from clinical trials investigating prescribed melatonin as an adjunctive therapy in patients with schizophrenia.

METHODS

A systematic literature review of MEDLINE (Ovid), Embase, PsychINFO, and PubMed on the 27/08/20; and CINAHL and Cochrane Library databases, was conducted. Inclusion criteria were: a peer-reviewed clinical trial published in English; included a group of patients with schizophrenia; used melatonin as an adjunctive therapy; and reported any outcome of any duration. Exclusion criteria were: neurodegenerative diseases, primary sleep disorders, co-morbid substance use or animal studies.

RESULTS

Fifteen studies were included in the current review with the following primary outcomes: sleep (n = 6), metabolic profile (n = 3), tardive dyskinesia (n = 3), cognitive function (n = 2) and benzodiazepine discontinuation (n = 1).

Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Australia

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 24, 2021
Peer-review started: February 24, 2021
First decision: July 4, 2021
Revised: July 12, 2021
Accepted: July 29, 2021
Article in press: July 29, 2021
Published online: August 19, 2021

P-Reviewer: Hosak L
S-Editor: Gao CC
L-Editor: A
P-Editor: Ma YJ



CONCLUSION
Adjunctive melatonin therapy has some positive outcomes for sleep, metabolic profile and tardive dyskinesia in patients with schizophrenia. No beneficial effect of melatonin was observed on outcomes of cognition or benzodiazepine discontinuation. Future studies utilizing larger samples and investigations specifically comparing the effect of melatonin as adjunctive therapy with different antipsychotics in patients with schizophrenia are required.

Key Words: Schizophrenia; Melatonin; Clinical trials; Sleep; Metabolic syndrome; Tardive dyskinesia

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Core Tip: This systematic review synthesized the results of clinical trials that have investigated the effect of exogenous melatonin as adjunctive therapy for patients with schizophrenia. Some positive outcomes were demonstrated for sleep improvement and attenuating antipsychotic-induced metabolic side effects. Future investigations are required to determine differential effects of melatonin when used in conjunction with a range of antipsychotic medications.

Citation: Duan C, Jenkins ZM, Castle D. Therapeutic use of melatonin in schizophrenia: A systematic review. *World J Psychiatr* 2021; 11(8): 463-476
URL: https://www.wjgnet.com/2220-3206/full/v11/i8/463.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i8.463

INTRODUCTION

Schizophrenia is a chronic psychiatric disorder characterized by a combination of positive (hallucinations and delusions) and negative symptoms affecting thought, perception, cognition and behaviour through complex mechanisms, often resulting in significant deterioration of function[1]. Along with the cardinal features of psychosis, associated side effects of medications and sleep dysfunction can cause lifelong impact on patients' quality of life[2].

Second-generation antipsychotics (SGAs) are the current standard for treating schizophrenia and related illnesses due to the comparatively lower rates of extrapyramidal side effects (EPS), as compared with first generation antipsychotics[3]. However, it has been demonstrated that EPS remain a potential side effect of SGAs[4]; tardive dyskinesia (TD) remains a risk even with these newer agents[5], with limited understanding of both the mechanisms and treatment options[6]. Furthermore, significant weight gain and an increased incidence of metabolic syndrome (MetS) and cardiovascular disease risk have also been established in association with certain SGA medications[7].

Sleep dysfunction is also common in people with schizophrenia, as demonstrated by poor sleep efficiency and disrupted circadian rhythms[8,9]. Studies have shown that there is decreased endogenous secretion of melatonin in patients with schizophrenia, and this pattern can persist despite improvement of sleep quantity and quality with antipsychotic agents[10]. Benzodiazepines (BZDs) are widely used to ameliorate sleep disruption in schizophrenia. While only recommended for short-term use, many patients remain on BZDs long-term, suffering additional effects including sedation, increased risk of falls, and cognitive impairment[11,12].

In an effort to address sleep dysfunction in individuals with schizophrenia, various studies have explored the use of exogenous melatonin. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenously produced hormone naturally secreted at night from the pineal gland in a circadian rhythm to promote sleep. Adjunctive administration of exogenous melatonin has been recognized to have therapeutic benefit in sleep disorders in the general population[13,14]; however, it remains relatively less explored in people with schizophrenia. Furthermore, melatonin has also demonstrated direct and indirect antioxidant and neuroprotective effects, suggesting various potential clinical uses for treatment in schizophrenia, notably EPS and MetS

[15].

The current review aims to synthesize the evidence from clinical trials investigating the effect of adjunctive use of melatonin on any outcome in individuals with schizophrenia.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to throughout the review.

Search strategy

The literature search was conducted online for papers in the English language with no restriction of publication date, using MEDLINE (Ovid), Embase, PsychINFO, and PubMed on 27/08/20; and CINAHL and the Cochrane Library on 28/08/20. Syntax was translated using Polyglot to search the databases appropriately. Search terms included the keywords of "schizophrenia", "melatonin" and with the following trade names — circadin, regulin, benedorm, melaxen or melovine, and "clinical trials" (of any type). Boolean operators OR was used to combine synonyms of the keywords, and AND was used to combine search terms. MeSH headings were specifically used for "schizophrenia", "melatonin" and "clinical trials" as well as searching for these terms in the title and abstract. Additional studies were identified from a manual search of the reference lists of included articles and registered clinical trials.

Inclusion criteria

The inclusion criteria for papers in this systematic review were: (1) A peer-reviewed research article published in English; (2) Included a group of participants with a diagnosis of schizophrenia (including its subtypes), paraphrenia, delusional psychoses, paranoid psychosis, psychosis not otherwise specified, schizophreniform disorder, schizotypal disorder or schizoaffective disorder; (3) A clinical trial using melatonin as adjunctive therapy; (4) Collected an outcome measure of any duration; and (5) Included original data in the paper. Exclusion criteria included review papers, meta-analyses, case reports, animal studies or studies with patient populations that included neurodegenerative diseases, organic causes of disease, and primary sleep disorders.

Study selection

Search results were exported to Endnote bibliographic management software, duplicates removed, and the remainder uploaded to Covidence systematic review software (www.covidence.org) by Duan C Two authors (Duan C, Castle D) independently screened records on title and abstract and then full text against the exclusion criteria and disagreements were resolved by discussion.

Data extraction and assessment of risk of bias

Two reviewers (Jenkins ZM and Duan C) independently extracted data and consensus was confirmed by a third reviewer (Castle D). Extracted data included information on study characteristics, objectives and outcomes. A meta-analysis was not performed as there were too few similarities across studies in terms of study methods and outcome measures. The risk of bias among included studies was assessed independently by two authors (Duan C and Jenkins ZM) using the Cochrane risk-of-bias tool for randomised trials[16] and consensus was confirmed by a third reviewer (Castle D). Studies were classified into three classes of quality, viz.: low, moderate or high risk of bias. The risk of bias was not used as an exclusion criterion in the selection of studies, to provide a complete overview of available data.

RESULTS

A total of 163 papers were identified from the search and an additional two papers were found from the reference list of the identified papers. Sixty eight duplicate records were excluded and the titles and abstracts of the remaining 97 papers were screened independently by two authors (Duan C and Castle D). After title and abstract screening, 25 papers were read in full and assessed for eligibility. A further 10 papers were excluded, leaving 15 papers included for qualitative synthesis (see Figure 1 for an

Figure Legends

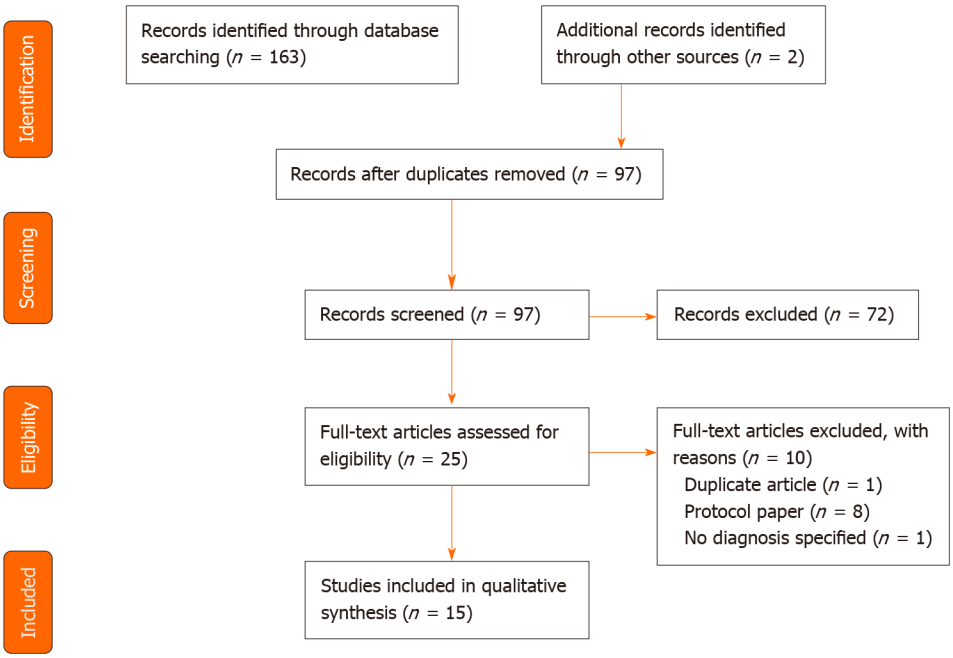


Figure 1 PRISMA flowchart.

overview of the study selection process).

Study characteristics

Characteristics of the 15 included studies for qualitative synthesis are shown in Tables 1-5. Four trials had a crossover design, two were open-label and nine utilized a randomized double-blind parallel design. The 15 trials included a total of 626 participants (351 male, 252 female, 23 not specified) with sample sizes ranging from 10-120. Diagnoses in the studies included 269 participants with schizophrenia, 268 with paranoid schizophrenia, 7 with disorganized schizophrenia, 27 with schizoaffective disorder and 55 with bipolar disorder (the bipolar disorder patients were part of a cohort including people with schizophrenia, hence their inclusion).

Risk of bias

One study was classified as at low risk of bias, nine were classified as having a moderate risk of bias and six were classified as being at high risk of bias (see outcome Tables for overall classification).

Outcome measures

Studies were grouped according to the following primary outcome measures: sleep (n = 6; see Table 1), metabolic profile (n = 3; see Table 2), TD (n = 3; see Table 3), cognitive function (n = 2; see Table 4) and BZD tapering (n = 1; see Table 5).

Sleep outcomes

Six studies primarily assessed the impact of melatonin therapy on sleep parameters in individuals with schizophrenia[17-22], see Table 1.

Two studies assessed the effect of controlled release melatonin formulation on sleep parameters over a three week period[17,18]; one demonstrated a significant improvement in sleep efficiency over three weeks of melatonin treatment, as compared to placebo[17] while the other reported worsened sleep efficiency, prolonged REM sleep latency and increased duration of wakefulness on the first night, as compared to the second night in participants who received melatonin[18]. Another investigation employed a patient-determined dosage of melatonin over a 15 d period; those who received melatonin had a decreased number of awakenings, increased sleep duration and superior self-report sleep parameters than controls[19].

The impact of melatonin on circadian rhythms was assessed by Mishra *et al*[20] according to change in serum and urinary melatonin levels, which increased over the trial period in participants who received melatonin therapy, compared with controls.

Table 1 Sleep outcomes

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings related to melatonin	Risk of bias
Shamir *et al* [18], 2000	14 (11 M, 3 F), 14 (11 M, 3 F)	Overall: 42.3 ± 13.1	2 mg CR melatonin or placebo/day for 3 wk	SZA (*n* = 2); Paranoid SCZ (*n* = 10); Disorganised SCZ (*n* = 2)	Diagnosis of chronic SCZ (as per DSM-IV criteria); poor sleep quality	Randomized, double-blind, crossover trial (1 wk washout)	Sleep latency (min), REM sleep (%), REM sleep latency (min), total sleep time (min), sleep efficiency (%), duration of wakefulness (min), stage 1 sleep (%), slow wave sleep (%)	REM Sleep latency (min): Melatonin: 1st night > 2nd night Sleep efficiency (%): Melatonin: 1st night < 2nd night Duration of wakefulness (min): Melatonin: 1st night > 2nd night Stage 1 sleep (%): Placebo: 1st night < 2nd night	High
Shamir *et al* [17], 2000	19 (12 M, 7 F); 19 (12 M, 7 F)	Overall: 42 ± 5	2 mg CR melatonin or placebo/day for 3 wk	SZA (*n* = 5); Paranoid SCZ (*n* = 9); Disorganised SCZ (*n* = 5)	Diagnosis of chronic SCZ (as per DSM-IV criteria); poor sleep quality	Randomized, double-blind, crossover trial (1 wk washout)	Urinary 6-SMT excretion, sleep efficiency (%), sleep latency (min), total sleep time (min), wake after sleep onset duration (min), fragmentation index (%), number of awakenings (N)	Sleep efficiency (%): Melatonin > Placebo	Some concerns
Suresh Kumar *et al* [19], 2007	20 (13 M, 7 F); 20 (14 M, 6 F)	38.4 ± 14.4; 36.0 ± 13.4	Patient determined dosage of melatonin or placebo for 15 d	Paranoid SCZ (*n* = 40)	Diagnosis of paranoid SCZ (as per DSM-IV criteria); illness duration < 1 yr; clinically stable; receiving same dose of haloperidol for the past month, insomnia present for past 2 wk	Double-blind, placebo-controlled study	Time taken to fall asleep (min), number of awakenings (n), duration of sleep (min), self-report sleep questionnaire	Number of awakenings (N): Melatonin < Placebo Duration of sleep (min): Melatonin > Placebo Self-report sleep questionnaire: Time to fall asleep, quality of sleep, depth of sleep, freshness on awakening, morning headache, morning mental dullness, mood, overall functioning were superior in Melatonin group *vs* Placebo	High
Mishra *et al* [20], 2020	PPS: 30 (15 M, 15 F); 30 (21 M, 9 F). PNS: 30 (21 M, 9 F); 30 (14 M, 16 F)	PPS: 38.6 ± 10.68; 34.0 ± 8.38. PNS: 34.97 ± 12.35; 37.87 ± 3.84	8 mg/d Ramelteon + monotherapy *vs* monotherapy alone for 4 wk	SCZ (*n* = 120). Patients were categorized into PPS (*n* = 60) and PNS (*n* = 60) groups based on PANSS scoring	Diagnosis of SCZ (as per DSM-5 criteria); aged between 18-65 yr; treatment naïve or had not taken treatment for 4 wk	Randomized, open-label, rater-blinded, parallel design clinical trial	Quality of sleep (PSQI), melatonin excretion (urinary melatonin 6aMTs), serum AANAT, symptom severity (PANSS)	Change in serum melatonin at 14:00 h: PPS and PNS: Melatonin > Control Change in serum melatonin 2 h after add on therapy: PPS and PNS: Melatonin > Control Change in urinary melatonin: PPS and PNS: Melatonin > Control Change in serum AANAT: PPS and PNS: Melatonin > Control	High

								PSQI: PPS and PNS: Melatonin > Control Change in PANSS total score: PPS and PNS: Total score improved Melatonin > Control; PPS: Decreased positive symptoms in Melatonin > Control; PNS: Decrease negative symptoms in Melatonin > Control	
Baandrup *et al*[22], 2016	20 (11 M, 9 F); 28 (18 M, 10 F)	47.7 ± 8.2; 45.9 ± 10.3	2 mg/d PR melatonin or placebo for 24 wk	Paranoid SCZ (n = 38), Non-paranoid SCZ (n = 2), SZA (n = 2), BP (n = 6)	Diagnosis of SCZ, SZA or BP (as per ICD-10 criteria); treated with 1 antipsychotic and 1 BZD for 3 m	Randomized, double-blind clinical trial	Actigraphy (sleep and 24 h rhythm activity variables)	-	Some concerns
Baandrup *et al*[21], 2016	28 (14 M, 14 F); 27 (15 M, 12 F)	48.8 ± 7.1; 49.1 ± 12.2	2 mg/d PR melatonin or placebo for 24 wk	Paranoid SCZ (n = 42), non-paranoid SCZ (n = 2), SZA (n = 3), BP (n = 8)	Diagnosis of SCZ, SZA or BP (as per ICD-10 criteria); treated with 1 antipsychotic and 1 BZD for 3 mo	Randomized, double-blind clinical trial	PSQI, polysomnography (n = 23; total sleep time, sleep latency, REM latency, time awake after sleep onset, number of awakenings, sleep architecture)	PSQI sleep quality: Melatonin > Placebo	Some concerns

AANAT: Aryl-alkylamine-N-acetyl-transferase; BP: Bipolar disorder; BZD: Benzodiazepine; CR: Controlled-release; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; F: Female; ICD-10: International Classification of Diseases, Tenth Revision; M: Male; PANSS: Positive and Negative Syndrome Scale; PNS: Predominant negative symptom group; PPS: Predominant positive symptom group; PR: Prolonged-release; PSQI: Pittsburgh sleep quality index; REM: Rapid eye movement; SCZ: Schizophrenia; SZA: Schizoaffective disorder.

Moreover, significant improvements in sleep (as measured by the PSQI) and symptoms of schizophrenia (as measured by the PANSS) were demonstrated by patients who received ramelteon as an add-on to antipsychotic therapy, compared to antipsychotic therapy alone[20].

Two publications reported different sleep outcomes from the same study whose primary aim was to observe the effect of melatonin on BZD discontinuation/reduction in patients with a diagnosis of schizophrenia or bipolar disorder. One reported no difference between add-on melatonin therapy on circadian rest-activity rhythms[22], compared to placebo. However, the other publication highlighted that participants who received melatonin reported superior subjective sleep quality than the placebo group[21].

Metabolic profile outcomes

Three studies assessed whether melatonin attenuates antipsychotic-induced metabolic side effects[23-25], see Table 2.

Modabbernia *et al*[24] investigated the impact of melatonin on patients with first episode schizophrenia. They reported significantly less increase in weight gain, body mass index (BMI) and total cholesterol over an eight week trial as well as significantly greater reductions in psychiatric symptoms (as assessed by the PANSS) in patients who received melatonin when initiating olanzapine, compared to placebo. Another

Table 2 Metabolic outcomes

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings related to melatonin	Risk of bias
Borba *et al* [23], 2011	14 (8 M, 6 F); 6 (5 M, 1 F)	49 ± 7; 56 ± 9	8 mg/d Ramelton or placebo for 8 wk	SCZ (*n* = 11), SZA (*n* = 9)	Diagnosis of SCZ (as per DSM-IV criteria); aged between 18-65 yr; BMI > 27 kg/m^2, insulin resistance or any component of metabolic syndrome or a BMI of > 30 kg/m^2	Double-blind, placebo-controlled pilot trial	Waist circumference (cm), abdominal fat as measured by DEXA, glucose metabolism, C-reactive protin, lipids, psychopathology (PANSS; HDRS, HCQoL), sleep quality (SSS, FSI, MOSSS), adverse effects (SATEE)	Total cholesterol; cholesterol-to-HDL ratio; LDL particle number: Melatonin < Placebo Adverse effects: Melatonin *vs* control group: drowsiness (57% *vs* 33%), heart burn (21% *vs* 0%), cough (21% vs 0%), akathisia (21% *vs* 0%), increased urinary frequency (14% *vs* 0%), problems with memory or concentration (21% *vs* 0%) Arthralgia/myalgia and anxiety: Placebo > Melatonin	High
Modabbernia *et al*[24], 2014	18 (13 M, 5 F); 18 (12 M, 6 F)	32.7 ± 7.3; 32.8 ± 8.2	3 mg/d melatonin + Olanzapine or placebo + Olanzapine for 8 wk	SCZ (*n* = 36)	Diagnosis of SCZ (as per DSM-IV criteria); aged between 18-65 yr; in their first-episode eligible for starting olanzapine	Randomized, double-blind, placebo-controlled, and parallel-group study	Anthropometric measures, BP, FBS, fasting plasma insulin, Psychopathology (PANSS)	Weight, BMI and Waist circumference: Melatonin < Placebo PANSS total score: Melatonin < Placebo	Some concerns
Romo-Nava *et al*[25], 2014	20 (10 M, 10 F); 24 (12 M, 12F)	Overall: 29.5 ± 8.3	5 mg/d CR melatonin or placebo for 8 wk	SCZ (*n* = 24); BP (*n* = 20)	Diagnosis of SCZ or BP type I (as per DSM-IV criteria); aged between 18-45 yr, initiated treatment with SGAs < 3 mo	Double-blind, placebo-controlled study	Anthropometric measures, body composition, BP, Lipids, Glucose, PANSS, CGI-S. BPD only: HDRS, YMRS. Schizophrenia only: CDS	Weight gain, waist circumference, DBP, fat mass, triglycerides: Melatonin (BP only) < Placebo	Some concerns

BMI: Body mass index; BP: Bipolar disorder; BP: Blood pressure; CDS: Calgary depression scale; CGI-S: Clinical Global Impression-Severity of Illness; CR: Controlled-release; DEXA: Dual-energy x-ray absorptiometry; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; F: Female; FBS: Fasting blood sugar; FSI: Fatigue scale inventory; HCQoL: Heinrichs-Carpenter Quality of Life Scale; HDL: High-density lipoprotein; HDRS: Hamilton Depression Rating Scale; LDL: Low-density lipoprotein; M: Male; MOSSS: Medical outcomes study sleep scale; PANSS: Positive and Negative Syndrome Scale; SATEE: Systematic assessment for treatment emergent events; SCZ: Schizophrenia; SGA: Second generation antipsychotics; SSS: Stanford sleepiness scale; SZA: Schizoaffective disorder; YMRS: Young mania rating scale.

investigation assessed the impact of melatonin on patients with schizophrenia or bipolar disorder taking SGAs[25]. For the group as a whole, melatonin attenuated weight gain, waist circumference increase and was associated with decreased diastolic blood pressure. However, subgroup analysis of participants with schizophrenia alone demonstrated no significant changes as a result of melatonin therapy[25].

Borba *et al*[23] investigated whether melatonin could attenuate the metabolic side-effects of antipsychotics in patients with a pre-existing BMI of above 27 kg/m^2 and at least one component of MetS. They demonstrated no change in anthropometric outcomes but did observe decreased total cholesterol, cholesterol-to-high-density lipoprotein ratio and low-density lipoprotein (LDL) particle number in those who received melatonin, compared to placebo[23]. Moreover, they reported significantly

Table 3 Tardive dyskinesia

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings related to melatonin	Risk of bias
Shamir *et al* [26], 2000	19 (8 M, 11 F); 19 (8 M, 11 F)	Overall: 74.0 ± 9.5	2 mg/d CR melatonin or placebo for 4 wk	SCZ (n = 19)	Diagnosis of SCZ of > 20 yr (as per DSM-IV criteria), TD > 5 yr, antipsychotic treatment > 10 yr	Double-blind, placebo-controlled, crossover trial (2 wk washout)	AIMS	-	Some concerns
Shamir *et al* [27], 2001	22 (11 F, 11 M); 22 (11 F, 11 M)	Overall: 64.2 ± 14.3	10 mg/d CR melatonin or placebo for 6 wk	SCZ (n = 22)	Diagnosis of SCZ and anti-psychotic-induced TD (as per DSM-IV criteria)	Double-blind, placebo-controlled, crossover trial (4 wk washout)	AIMS	AIMS: Melatonin < Placebo	Some concerns
Castro *et al* [28], 2011	7; 6 (sex NR)	Overall: 59.9 ± 2.7	20 mg/d melatonin or placebo for 12 wk	SCZ (n = 11); BP (n = 2)	Diagnosis of neuroleptic-induced TD (as per DSM-IV criteria)	Randomized, double blind, placebo-controlled pilot study	AIMS; BPRS	-	High

AIMS: Abnormal Involuntary Movement Scale; BP: Bipolar disorder; BPRS: Brief psychiatric rating scale; CR: Controlled-release; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; F: Female; M: Male; NR: Not reported; SCZ: Schizophrenia; TD: Tardive dyskinesia.

Table 4 Cognitive function

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings related to melatonin	Risk of bias
Shirayama *et al*[29], 2014	10 (NR); -	42.5 ± 7.3	8 mg/d melatonin for 6 mo	SCZ (n = 10)	Diagnosis of SCZ (as per DSM-IV criteria); symptoms stable for 3 mo	Open-label study	TMT (A and B), WCST, VFT, Stroop Test, DSPDT, IGT, RAVLT	RAVLT (total, delayed recall and recognition): Improved at 6-mo compared to baseline	High
Baandrup *et al*[30], 2017	40 (21 M, 19 F); 40 (24 M, 16 F)	47.4 ± 8.6; 49.0 ± 12.1	2 mg/d CR melatonin or placebo for 24 wk	Paranoid SCZ (n = 62), non-paranoid SCZ (n = 6), SZA (n = 3), BP (n = 9)	Diagnosis of SCZ, SZA or BP (as per ICD-10 criteria); treated with 1 antipsychotic and 1 BZD for 3 mo	Randomized, double-blind clinical trial	BACS (domains: verbal memory, working memory, motor speed, verbal fluency, letter fluency, attention and processing speed, executive function), WHO-Five WBI, SWN, PSP, UKU, PANSS	-	Low

BACS: Brief assessment of cognition in schizophrenia; BP: Bipolar disorder; BZD: Benzodiazepine; CR: Controlled-release; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSPDT: Digit span distraction test; F: Female; ICD-10: International Classification of Diseases, Tenth Revision; IGT: Iowa gambling task; M: Male; NR: Not reported; PANSS: Positive and negative syndrome scale; PSP: Personal and social performance scale; RAVLT: Rey auditory verbal learning test; SCZ: Schizophrenia; SWN: Subjective wellbeing under neuroleptic treatment scale; SZA: Schizoaffective disorder; TMT: Trail-making test; part A and part B; UKU: Udvalget for Kliniske Undersoegelser side effect rating scale; VFT: Verbal fluency test; WCST: Wisconsin card sorting test; WHO-Five WBI: WHO-five wellbeing index.

lower levels of arthralgia/myalgia and anxiety, yet significantly more side effects of drowsiness (57% *vs* 33%), heart burn (21% *vs* 0%), cough (21% *vs* 0%), akathisia (21% *vs* 0%), increased urinary frequency (14% *vs* 0%), and problems with memory or concentration (21% *vs* 0%) in those who received melatonin in comparison with those on placebo[23].

Table 5 Benzodiazepine discontinuation

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings	Risk of bias
Baandrup *et al*[12], 2016	42 (23 M, 19 F); 44 (25 M, 19 F)	47.9 ± 8.7; 49.4 ± 12.3	2 mg/d PR melatonin or placebo for 24 wk	Paranoid SCZ (n = 67), Non-paranoid SCZ (n = 6), SZA (n = 3), BP (n = 10)	Diagnosis of SCZ, SZA or BP (as per ICD-10 criteria); treated with 1 antipsychotic drug and 1 BZD drug for 3 mo; able to understand Danish	Randomized, double-blind clinical trial	Mean daily dosage of BZD, pattern of BZD dosage, BZD cessation proportion, BWSQ-2	-	Some concerns

BP: Bipolar disorder; BWSQ-2: Benzodiazepine Withdrawal Symptom Questionnaire; BZD: Benzodiazepine; ICD-10: International Classification of Diseases, Tenth Revision; PR: Prolonged release; SCZ: Schizophrenia; SZA: Schizoaffective disorder.

TD

Three studies investigated the impact of melatonin therapy on symptoms of TD[26-28], see Table 3.

The use of 2 mg/d adjunctive melatonin therapy over a four week period did not affect severity of TD in an initial study by Shamir *et al* [26]. However, a follow-on study from the same investigators found that 10 mg/d of melatonin over a six week period was associated with a significant decrease in TD severity (as measured by the Abnormal Involuntary Movement Scale; AIMS) in patients with chronic schizophrenia, as compared to placebo[27]. In a more recent study, however, Castro *et al*[28] used 20 mg/d of melatonin over a 12 wk period, yet did not observe any difference from placebo in terms of TD symptoms.

Cognitive function

Two studies investigated the impact of melatonin on cognitive function in people with schizophrenia, over a period of 24 wk[29,30], see Table 4.

The only significant change in cognitive function associated with melatonin treatment was improved memory on a verbal learning task post-treatment (8 mg/d for six months), as compared to baseline levels in one of these studies[29]. In contrast, Baandrup *et al*[30] did not report any change in any domain of cognitive functioning — as assessed by the Brief Assessment of Cognition in Schizophrenia (BACS) cognitive battery — in patients receiving 2 mg/d prolonged-release melatonin for 24 wk.

Benzodiazapine discontinuation

Baandrup *et al*[21,22,30] investigated the impact of melatonin during discontinuation or reduction of BZDs and reported various outcomes in four papers, three of which are reported above. Overall, they found that add-on melatonin did not impact average BZD dosage, dosage pattern, cessation proportions or BZD withdrawal symptoms over their 24-wk trial, see Table 5[12].

DISCUSSION

The current review provides a synthesis of investigations using melatonin for individuals with schizophrenia, across a diverse range of outcomes. The various outcomes identified are discussed below.

Sleep

The impact of melatonin on sleep function was the most commonly reported outcome in the current review, with some positive outcomes. Two studies assessed the efficacy of melatonin in improving sleep efficiency (defined as proportion of time asleep over total time in bed). One demonstrated improved efficiency[17] while one reported worsened sleep efficiency[18]. However, the worsened sleep efficiency (and accompanying prolonged REM sleep latency and increased duration of wakefulness) was a comparison between sleep parameters on the first night to the second night of the study. The study objective was to investigate the impact of melatonin on 'the first

night effect (FNE)', whereby individuals have a tendency to experience poorer sleep quality on the first night of a sleep evaluation study[18]. Therefore, while this study demonstrated that melatonin does not ameliorate the FNE, conclusions cannot be drawn about extended sleep efficiency.

The only study in the current review that permitted a patient-determined dosage of melatonin revealed a significantly lower number of night-time awakenings, a longer duration of sleep and improved subjective sleep quality in patients with schizophrenia and comorbid insomnia, as compared to placebo[19]. While the modal dose of melatonin over the trial was 3 mg/d, the authors conceded that conclusions could not be made regarding the optimal dose of melatonin for improved sleep outcomes. Moreover, they did not employ an objective measure of sleep, such as polysomnographic or actigraphic assessments, recommending that further investigation is required[19].

The impact of melatonin on circadian rhythm was assessed in two studies; increased objective measures of serum and urinary melatonin were observed in patients who received melatonin[20], yet actigraphic observations of circadian rhythm revealed no change with melatonin treatment[22]. However, the actigraphic assessments were taken in patients who were concurrently discontinuing BZD medication, limiting generalisation. The same investigation reported improved subjective sleep quality in patients tapering off BZDs[21], suggestive of some beneficial impacts of melatonin.

Overall, melatonin's main indication has been to treat disorders of sleep based on its physiological regulatory effects. In mental health populations, there has been increasing use in treatment of disorders that have a sleep dysfunction component[31]. In patients with schizophrenia, exogenous melatonin induced secretion of endogenous melatonin in a single study and improved sleep efficiency in another. Future replications utilizing a controlled melatonin dosage, free from the impact of BZD discontinuation, are required in order to clarify the indications for melatonin on sleep in people with schizophrenia.

Metabolic profile outcomes

The efficacy of melatonin in ameliorating metabolic side effects of antipsychotics among patients with schizophrenia was explored in three studies; two of which reported some benefits[23,24].

Adjunctive treatment of melatonin was effective in attenuating weight gain in first episode schizophrenia patients who were initiating treatment with olanzapine[24]. However, no significant benefit of melatonin on body weight were observed in two separate studies of patients with an established history of antipsychotic treatment[23,25]. A tentative interpretation of these findings is that the use of melatonin in conjunction with the initiation of antipsychotic treatment may assist in the initial weight gain associated with first episode psychosis and initiation of antipsychotics[32,33], but further studies are required.

The only other beneficial metabolic outcome was an improvement in total cholesterol and LDL-particle number in participants who received ramelteon in a pilot study[23]. However, the inclusion criteria for that study specified patients with a pre-existing BMI of above 27 and a component of the MetS, therefore it may be that melatonin is more effective for those with poorer initial metabolic health. There is also the possibility of the finding simply reflecting regression to the mean. While no significant beneficial impact on lipid profile was seen in the larger studies included in this review, there was a trend towards improvement in triglyceride levels in first episode patients[24]; further studies are required.

Given that some metabolic outcomes were improved in patients with schizophrenia [23,24] and bipolar disorder[25] taking antipsychotic medication, and a recent animal study demonstrated efficacy of melatonin in attenuating antipsychotic-induced weight gain[34], there are positive indications for the adjunctive use of melatonin. It was also suggested that the variation in efficacy may be partly explained by the relative metabolic risk associated with different antipsychotics[25]. Melatonin reduced weight gain in patients receiving medium risk antipsychotics (quetiapine and risperidone), an effect that was not seen in patients receiving high risk antipsychotics (clozapine and olanzapine)[25]. Therefore, future studies should also investigate the differential impact of adjunctive melatonin therapy on individual antipsychotic medications.

TD

Three studies in the current review assessed the impact of melatonin on TD severity using the AIMS, with one group suggesting that both duration and dosage of melatonin therapy are pertinent to alleviating symptoms of TD. Shamir *et al*[27] initially found no beneficial impact of a low dose of melatonin on TD, yet their later

investigation using a higher dose of melatonin for a prolonged period suggested clinical efficacy for symptoms of TD[27]. However, these results were not replicated in a further study[28]. While melatonin has demonstrated efficacy in attenuating symptoms of TD in animal models, it has been suggested that this may be due to anti-dopaminergic activity masking the movements, as opposed to treating TD *per se*[35].

Cognitive function

It is well established that schizophrenia is associated with impairments across a wide range of cognitive domains[36]. The current review identified only one study whose primary objective was to observe the effect of add-on melatonin on cognitive function in patients with schizophrenia[29]. While a test of memory function (RAVLT) improved over six months in patients with schizophrenia, this improvement was in comparison to baseline assessments rather than controls[29]. Moreover, given the study design was open-label and conducted in a small sample size, this result requires further replication. Cognitive outcomes were assessed as a secondary outcome in a separate study whose primary objective was to observe the efficacy of melatonin as facilitator of reduction or discontinuation of chronic use of BZDs[30]. No cognitive improvements were observed in the cognitive battery (BACS), consistent with the literature suggesting that pharmacological adjuncts are yet to prove effectiveness in significantly enhancing cognition in patients with schizophrenia[37].

BZD discontinuation

One study in the current review investigated the effects of melatonin in facilitating reduction or discontinuation of chronic use of BZDs in patients with schizophrenia [12], concluding that adjunctive melatonin had no significant effect on BZD dosage or cessation over 24 wk. Moreover, any interpretation of secondary outcomes from this investigation would need to be considered within the context of BZD withdrawal.

Limitations

The interpretations from the current review are limited by the small sample sizes of included studies. Melatonin formulations and dosages differed across studies. Moreover, risk of bias assessment indicated that only one study was deemed at low risk of bias, with the remainder carrying moderate or high risk of bias. Furthermore, some samples included patients with diagnoses of schizophrenia and bipolar disorder, making it difficult to delineate the effect of melatonin for schizophrenia alone. It remains an open question whether efficacy of melatonin for sleep in people with schizophrenia endures over the longer term: future studies should address this important topic.

CONCLUSION

The current review synthesized the results of clinical trials investigating the effect of adjunctive melatonin therapy on any outcome in patients with schizophrenia. To date, investigated outcomes include sleep function, metabolic benefits, TD attenuation, cognitive function and as an adjunct to BZD discontinuation. Positive outcomes were demonstrated for the use of melatonin in improving sleep efficiency and circadian rhythm as well as certain metabolic outcomes, specifically in first-episode patients initiating antipsychotic treatment. One study reported benefit for the use of melatonin in attenuating TD, but this was not found in other studies. There was no observed benefit for the use of melatonin in improving cognitive function or facilitating BZD discontinuation in individuals with schizophrenia. Given that the pharmacokinetics of melatonin and interactions with other drugs are unclear, future studies investigating these in relation to specific antipsychotic medications are required. Moreover, the range of melatonin dosage used and the duration of the studies in the current review highlights that there is currently no standardized melatonin recommendation and the effects of contamination and different formulations are unknown.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia is a chronic psychiatric condition consisting of positive and negative

symptoms causing significant impacts on life. Current treatment includes second-generation antipsychotics (SGAs), the use of which is associated with side effects including: increased metabolic risk, sleep dysfunction and extrapyramidal side effects (EPS). Exogenous melatonin has been demonstrated to attenuate sleep dysfunction in the general population, however its indication in schizophrenia has been relatively unexplored. The proven antioxidant and neuroprotective effects of melatonin suggest potential for therapeutic benefit in adjunctive treatment of schizophrenia, especially in attenuating side effects associated with SGAs.

Research motivation

Current therapeutic treatment for schizophrenia often causes side effects including increased cardiovascular and metabolic risk, sleep dysfunction and EPS. Adjunctive use of melatonin has been suggested to benefit sleep disturbances, however its indication in schizophrenia has remained unclear. Therefore, we synthesized the current evidence for the effect of adjunctive use of melatonin on any outcome in individuals with schizophrenia.

Research objectives

To synthesize clinical trials conducted to date that have investigated the use of melatonin as an adjunctive therapy for individuals with schizophrenia in improving any therapeutic outcome.

Research methods

A systematic literature search was conducted on MEDLINE (Ovid), Embase, PsychINFO, PubMed, CINAHL and Cochrane Library for clinical trials using melatonin as an adjunctive therapy that included a group of patients with schizophrenia. PRISMA guidelines were adhered to and the Cochrane risk-of-bias tool for randomized controlled trials was used by two authors to assess the trials independently, with consensus confirmed by a third reviewer.

Research results

A total of 15 trials were included for qualitative synthesis after assessing for eligibility and removing duplicates. The trials assessed the following primary outcomes: sleep (n = 6), metabolic profile (n = 3), tardive dyskinesia (n = 3), cognitive function (n = 2) and benzodiazepine discontinuation (n = 1).

Research conclusions

Positive outcomes were demonstrated for the use of melatonin in improving sleep efficiency and certain metabolic outcomes, specifically in first-episode patients initiating antipsychotic treatment. Currently, there is limited therapeutic indication for the use of melatonin in treatment of tardive dyskinesia, cognitive function or facilitating benzodiazepine discontinuation. Limitations included small sample sizes and no standardization of the duration and/or dosage of adjunctive melatonin used.

Research perspectives

Future studies are required to confirm these improvements, determine the pharmacokinetic interactions of melatonin with specific antipsychotic medications and develop a standardized duration and dosage of adjunctive melatonin treatment. Moreover, a long-term safety and efficacy profile remains to be determined.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 August 19; 11(8): 477-490

DOI: 10.5498/wjp.v11.i8.477

ISSN 2220-3206 (online)

META-ANALYSIS

Hypomanic/manic switch after transcranial magnetic stimulation in mood disorders: A systematic review and meta-analysis

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Author contributions: Miuli A, Sepede G, Pettorruso M, Martinotti G and di Giannantonio M designed the research study; Miuli A, Stigliano G, Mosca A, Di Carlo F, d'Andrea G, Lalli A and Spano MC performed the research; Miuli A and Sepede G analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an

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Abstract

BACKGROUND

Nowadays there is an increasing use of transcranial magnetic stimulation (TMS) both in neurological and psychiatric fields. After Food and Drug Administration approval of TMS for the therapy of treatment-resistant depression, TMS has been widely used in the context of mood disorders (MD). However, growing reports regarding the possibility of developing hypomanic/manic switch (HMS) have generated concern regarding its use in MDs.

AIM

To investigate the actual risk of developing HMS due to TMS in the treatment of MD.

METHODS

We led our research on PubMed, Scopus and Web of Science on March 22, 2020, in accordance to the PRISMA guidelines for systematic review. Only double blind/single blind studies, written in English and focused on the TMS treatment of MD, were included. A meta-analysis of repetitive TMS protocol studies including HMS was conducted using RevMan 5.4 software. The assessment of Risk of Bias was done using Cochrane risk of bias tool. This protocol was registered on PROSPERO with the CRD42020175811 code.

RESULTS

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 16, 2021
Peer-review started: February 16, 2021
First decision: March 16, 2021
Revised: March 24, 2021
Accepted: July 20, 2021
Article in press: July 20, 2021
Published online: August 19, 2021

P-Reviewer: Tajiri K
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Guo X

Twenty-five studies were included in our meta-analysis: Twenty-one double blind randomized controlled trials (RCT) and four single blind-RCT (no. of subjects involved in active stimulation = 576; no. of subjects involved in sham protocol = 487). The most frequently treated pathology was major depressive episode/major depressive disorder, followed by resistant depression, bipolar depression and other MD. The majority of the studies used a repetitive TMS protocol, and the left dorsolateral prefrontal cortex was the main target area. Side effects were reported in eight studies and HMS (described as greater energy, insomnia, irritability, anxiety, suicidal attempt) in four studies. When comparing active TMS *vs* sham treatment, the risk of developing HMS was not significantly different between conditions.

CONCLUSION

Applying the most usual protocols and the appropriate precautionary measures, TMS seems not to be related to HMS development.

Key Words: Hypomanic/manic switch; Transcranial magnetic stimulation; Active *vs* sham comparison; Mood disorders; Adverse event; Safety

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Core Tip: Transcranial magnetic stimulation (TMS) has been widely used in the context of mood disorders. The purpose of this review/meta-analysis was to examine the risk of developing a hypomanic/manic switch (HMS) during active TMS treatment of mood disorders. Twenty-five double blind/single blind studies were included in the quantitative synthesis. When comparing active TMS *vs* sham treatment, we did not find any significant difference in the risk of developing HMS between conditions. So, we can conclude that, applying the appropriate precautionary measures, TMS seems not to be related to HMS development.

Citation: Miuli A, Sepede G, Stigliano G, Mosca A, Di Carlo F, d'Andrea G, Lalli A, Spano MC, Pettorruso M, Martinotti G, di Giannantonio M. Hypomanic/manic switch after transcranial magnetic stimulation in mood disorders: A systematic review and meta-analysis. *World J Psychiatr* 2021; 11(8): 477-490
URL: https://www.wjgnet.com/2220-3206/full/v11/i8/477.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i8.477

INTRODUCTION

Non-invasive brain stimulation is a complex of neuromodulation techniques that have a therapeutic effect by stimulating the nervous system[1]. Transcranial magnetic stimulation (TMS) uses the principle of magnetic induction to modulate the neural circuitry[2]. Some electrical currents pass through a coil to induce repetitive magnetic field pulses that, if applied on the scalp, can stimulate target brain regions depolarizing the underlying neurons[3]. Depending on the stimulation frequency, cortical activity can be inhibited [low frequencies (LF) ≤ 1 Hz] or improved [high frequencies (HF) ≥ 5 Hz][4].

There are different protocols based on the number of pulses administrated (single pulses or paired pulses TMS)[5] or specific intervals between trains [like intermittent theta burst stimulation (TBS)[6], but one of the most used protocol is repetitive TMS (rTMS) where the pulses are applied as repetitive stimulation trains set at a specific frequency[4].

The use of rTMS has found an application in the field of substance[7] and non-substance addiction[8] but also in major psychiatric disorders such as post-traumatic stress disorder, schizophrenia and obsessive–compulsive disorder and in suicide[9-12]. It has also been used in the treatment of bipolar disorder, with good results in the treatment of depressive states and controversial results in mania[13]. In particular, TMS was approved by Food and Drug Administration in 2007 as a therapy for the treatment resistant depression (TRD)[14]. The standard protocol used in the treatment

of depression provides 75 trains *per* session for a total of 3000 pulses over about 35 min generated at 120% of resting motor threshold at 10 Hz, train duration of 4 s[14,15].

The role of the left dorsolateral prefrontal cortex (LDLPFC) in the pathophysiology of depression has been widely demonstrated with numerous evidences from functional imaging[16]. TMS, stimulating the DLPFC, is able to increase the neuronal excitability and to induce growth of the new connections having an antidepressant effect[17], both as a single treatment and as an add-on to antidepressants[18]. Some evidence, in fact, suggests that it may increase or decrease the neural excitability producing lasting changes in the efficiency of the synaptic transmission known as long-term potentiation and long-term depression[3,19].

When provided within recommended guidelines[20], rTMS is a very safe and well-tolerated technique both in the elderly[21] and in children[22] and has shown a favorable profile compared to antidepressant medications[23,24].

The most common side effects of TMS are headache, neck pain and local pain during the treatment at the site of stimulation[25]. The serious side effects are typically uncommon: Those reported were seizures, noted in less than 1% of healthy subjects and in patients with neurological morbidities and/or epilepsy[20,26], and hearing impairment, preventable with adequate protection[27]. Another potential side effect of TMS is the development of hypomanic/manic switch (HMS)[24,28].

HMS is one of the most critical events in bipolar disorder, affecting the severity of illness and being associated with an increased risk of suicide[29]. It can be linked to antidepressant treatments, and therefore antidepressants should be associated with mood stabilizers in bipolar patients[30]. Following the Diagnostic and Statistical Manual of Mental Disorders-5 criteria, hypomanic symptoms subsiding after stopping the antidepressants are called "antidepressant-induced hypomania", otherwise the episode can be defined as a true HMS[31,32].

During TMS treatment, cases of HMS were described in some reports[33,34], but to date the risk of TMS-induced HMS has not been yet extensively reported.

The purpose of this study was therefore to examine the actual risk of developing HMS due to TMS in the treatment of mood disorders, providing both qualitative and quantitative synthesis.

MATERIALS AND METHODS

The statistical methods of this study were reviewed by Gianna Sepede (GSe), who has qualified experience in Biomedical Statistics, Systematic Reviews and Meta-analysis.

Our systematic review was conducted to study the risk of developing HMS in a population of patients with mood disorders. We led our research on PubMed, Scopus and Web of Science (WoS) on March 22, 2020 using the following search strategy: (1) PubMed: (TMS OR Transcranial Magnetic Stimulation) AND (side effect OR adverse event) AND (depression OR manic OR bipolar OR hypomanic OR switch) NOT review NOT (animal OR rat OR mouse); (2) Scopus: [TITLE-ABS-KEY (tms) OR TITLE-ABS-KEY (transcranial AND magnetic AND stimulation) AND TITLE-ABS-KEY (side AND effect) OR TITLE-ABS-KEY (adverse AND event) AND TITLE-ABS-KEY (depression) OR TITLE-ABS-KEY (manic) OR TITLE-ABS-KEY (bipolar) OR TITLE-ABS-KEY (hypomanic) OR TITLE-ABS-KEY (switch) AND NOT TITLE-ABS-KEY (review) AND NOT TITLE-ABS-KEY (animal) OR TITLE-ABS-KEY (rat) OR TITLE-ABS-KEY (mouse)]; and (3) WoS: [(TMS OR Transcranial Magnetic Stimulation) AND (side effect OR adverse event) AND (depression OR manic OR bipolar OR hypomanic OR switch) NOT review NOT (animal OR rat OR mouse)]

All the procedures are in accordance with the PRISMA guidelines for systematic review[35]. Exclusion criteria, both for the first and the second phase of the screening, were: (1) Non-original research (*e.g.*, review, commentary, editorial, book chapter); (2) Non full-text article (*e.g.*, meeting abstract); (3) Language other than English; (4) Animal/*in vitro* studies; (5) Non double blind randomized controlled trial (DB-RCT) or single blind-RCT (SB-RCT) design; (6) Use of other neuromodulation techniques (*e.g.*, tDCS, MST); (7) Treatment of other conditions unrelated to mood disorders and (8) Data not reported.

We found 702 articles (PubMed = 80; Scopus = 338; WoS = 284). After removing the duplicates (No = 239), we screened 463 records and, of all these, 80 were non-original articles (review, meta-analysis, commentary, letter to the editor without data available), 267 were not related to the focus of the review (animal/*in vitro* studies, no DB-RCT or SB-RCT design, open label study, no sham comparison, no mood disorder treated, no TMS treatment), and 23 were not written in English. Out of 93 articles

assessed for eligibility, 46 were case report/series, 19 were not relevant to the subject (no DB-RCT or SB-RCT design, open label study, no sham comparison, no mood disorder treated, no TMS treatment) and three articles were not available. Twenty-five articles, finally, were taken into consideration for qualitative synthesis.

The process was conducted individually by AM, GS and Amo, creating an Excel database. For doubtful cases, the eligibility was discussed with GM, MP or MdG. These research methods were approved by PROSPERO (CRD42020175811 identification code). The method is summarized in Figure 1.

Risk of bias

The assessment of risk of bias was measured independently by AM, GS and AMo using the Cochrane risk of bias tool (Figure 2)[36]. This result was discussed with GSe and evaluated by MP, GM and MdG.

Quantitative analysis

The main outcome was to calculate the risk of developing HMS with TMS therapy in a population with mood disorders, so an active *vs* sham treatment comparison was conducted. The meta-analysis was performed using Review Manager Software v 5.4 [37]. Provided that HMS is an uncommon side effect and in order to include the studies with an event frequency of zero, a risk difference (RD) and not a risk ratio was applied[38,39].

The RD of the HSM for each individual article was calculated and, therefore, computed together obtaining a Fixed Effect with 95% confidence interval (CI). Statistical significance was set for values of $P < 0.05$.

We used I^2 to calculate the heterogeneity of the studies: $I^2 < 30\%$ low heterogeneity; $30\% < I^2 < 60\%$ moderate heterogeneity; $60\% < I^2 < 75\%$ substantial heterogeneity; $I^2 > 75\%$ high heterogeneity[40].

In case of heterogeneous results, a meta-analysis *per* categorical variable level was performed to evaluate the influence of categorical moderators on study outcomes. The final result is shown in the Forest Plot.

In order to assess potential publication bias, a funnel plot of study effect sizes was visually inspected for asymmetry (Figure 3).

RESULTS

All the characteristics of the included articles are described in Table 1.

We obtained a total of 25 studies for our systematic review. Following our inclusion and exclusion criteria all of them were DB-RCTs except for four SB-RCTs[41-44].

Among the included studies, the most frequently treated pathology was major depressive episode (No = 10)[42,44-52] followed by resistant depression (No = 5)[43,44,53-55], bipolar depression (No = 4)[41,43,44,56], major depressive disorder (No = 3)[57-59] and other mood disorders (No = 6)[60-65].

We found four studies allowing the use of antidepressants: Fluoxetine[49], paroxetine[46], amitriptyline[48] and not specified molecules (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors) [45].

The majority of the studies had LDLPFC as the main target area (No = 19)[41,42,44-53,56-60,62,64], although other areas have been stimulated, in particular: Right DLPFC (RDLPFC; No = 4)[44,53,55,65], bilateral (LDLPFC and RDLPFC; No = 4)[43,54,55,63] and other area (No = 1)[42], specifically the anterior cingulate.

The most used coil was the figure eight coil (No = 16)[41-49,51,53-56,59-63,65]. Other coils used were the double cone coil (No = 1)[42] and the H1 coil (No = 3)[52,58,64]. The number of studies where the type of coil was not specified were two[50,57].

The duration of the treatment also differed greatly in our sample: Most of our sample received 2 wk of acute treatment (No = 10)[41,43-47,49,51,59,61]. Other durations of acute treatment were 3 wk (No = 3)[42,54,56], 4 wk (No = 4)[48,52,58,65], 5 wk (No = 2)[50,63], 6 wk (No = 3)[53,55,64], only 1 wk (No = 2)[57,60] and less than 1 wk in just one study[62].

About the TMS technique used, most have used a rTMS protocol (No = 23)[41-55,57,59-63,65]. Other protocols were TBS at 50 Hz (No = 2)[56,59] and deep TMS (dTMS) at 18 Hz (No = 2)[58,64].

rTMS protocols

Based on the Hz set, the sample can be divided between those who have used LF

Table 1 Characteristics of the studies included in the systematic review

Ref.	Population (No total, No male, No subgroups, age ± SD of the subgroups)	Type of treatment	Protocol (type, Hz, No pulses/session, RMT, coil type, target area, treatment duration)	Mood Disorder Sub-type	Reported adverse events (yes, no, NS)	HMS (No tot)	Drop out due to HMS
Trevizol *et al* [53], 2019-A	Active TMS, No = 20, age = 66.8 ± 5.8 (M = 13). Sham = 12, age = 64.1 ± 3.7 (M = 3)	Only TMS	rTMS, 1 Hz, 465 impulse/session, 120% RMT, B-65 figure-8 coil, RDLPFC, 15 session AND rTMS, 10 Hz, 750 impulse/session, 120% RMT, B-65figure-8 coil, LDLPFC, 15 session	Late-life TRD	No (light and not worth mentioning)	0	no
Trevizol *et al* [53], 2019-B	Active TMS, No = 11, age = 66.1 ± 8.5 (M = 4). Sham = 12, age = 64.1 ± 3.7 (M = 3)	Only TMS	rTMS, 10 Hz, 1450 impulse/session, 120% RMT, B-65 figure-8 coil, LDLPFC, 15 session	Late-life TRD	Yes (TMS, No = 2; SHAM, No = 0)	1	no
Rao *et al*[65], 2019	Active TMS, No = 13, age = 39.8 ± 14.2 (M = 5). Sham = 17, age = 40.2 ± 14.6 (M = 11)	Only TMS	rTMS, 1 Hz, 12000 impulse/session, 110% RMT, B-65 figure-8 coil, RDLPFC, 20 session	MDE after traumatic Brain Injury	No (light and not worth mentioning)	0	no
Matsuda *et al* [64], 2020	Active TMS, No = 20, age = 43.4 ± 5.5 (M = 18). Sham = 20, age = 45.2 ± 7 (M = 19)	Only TMS	dTMS, 18 Hz, 1980 impulse/session, 120% RMT, H1 coil, LDLPFC, 30 session	Depression NS	No (light and not worth mentioning)	0	no
Li *et al*[59], 2020-A	Active TMS, No = 35, age = 47.1 ± 13.8 (M = 11). Sham = 35, age = 47.1 ± 12.4 (M = 11)	Only TMS	rTMS, 10 Hz, 1600 impulse/session, 100% RMT, figure-8 coil, LDLPFC, 10 session	Recurrent major depression	Yes (TMS, No = 12; SHAM, No = 8)	0	no
Li *et al*[59], 2020-B	Active TMS, No = 35, age = 47.1 ± 14.2 (M = 12). Sham = 35, age = 47.1 ± 12.4 (M = 11)	Only TMS	piTMS, 50 Hz, 1800 impulse/session, 80% RMT, figure-8 coil, LDLPFC, 10 session	Recurrent major depression	Yes (TMS, No = 9; SHAM, No = 8)	0	no
Bulteau *et al* [56], 2019	Active TMS, No = 12, age = 52.7 (M = 5). Sham = 14, age = 53.1 (M = 10)	Only TMS	iTBS, 50 Hz, 990 impulse/session, 80% RMT, figure-8 coil, LDLPFC, 15 session	BD	No	0	no
Siddiqi *et al* [63], 2019	Active TMS, No = 9, age = 43 ± 13 (M = 7). Sham = 6, age = 50 ± 18 (M = 4)	Only TMS	Bilateral rTMS, 10 Hz, 4000 impulse/session, 120% RMT, B-65 figure-8 coil., LDLPFC, 25 session AND Bilateral rTMS, 1 Hz, 1000 impulse/session, 120% RMT, B-65figure-8 coil, RDLPFC, 25 session	MDE after traumatic Brain Injury	Yes (TMS, No = 9; SHAM, No = 0)	0	no
Kaster *et al* [52], 2018	Active TMS, No = 25, age = 65.0 ± 5.5 (M = 17). Sham=27, age = 65.4 ± 5.5 (M = 15)	Only TMS	rTMS, 18 Hz, 6012 impulse/session, 120% RMT, H1 coil, LDLPFC, 20 session	Late-life MDE	No (light and not worth mentioning)	1	no
Xie *et al*[57], 2015	Active TMS, No = 35, age=65.3 ± 5.1 (M = 12). Sham = 26, age = 64.7 ± 4.2 (M = 8)	rTMS + shuganjieyu	rTMS, 10 Hz, NS impulse/session, 30% RMT, B-65NS coil, LDLPFC, 5 session	MDD	Yes (TMS, No = 14; SHAM, No = 13)	0	no
Levkovitz *et al* [58], 2015	Active TMS, No = 101, age = 45.1 ± 11.7 (M = 53). Sham = 111, age = 47.6 ± 11.6 (M = 58)	Only TMS	dTMS, 18 Hz, 1980 impulse/session, 120% RMT, H1 coil, LDLPFC, 20 session	MDD	No (light and not worth mentioning)	0	no
Kreuzer *et al* [42], 2015-A	Active TMS, No = 13, age = 43.5 ± 10.3 (M = 8). Sham = 12, age = 43.8 ± 10.5 (M = 4)	Only TMS	rTMS, 10 Hz, 2000 impulse/session, 110% RMT, B-65 double cone coil, Anterior Cingulate, 15 session	MDE	Yes (TMS, No = 7; SHAM, No = 8)	0	no
Kreuzer *et al* [42], 2015-B	Active TMS, No = 15, age = 46.1 ± 9.5 (M = 7). Sham = 12, age = 43.8 ± 10.5 (M = 4)	Only TMS	rTMS, 10 Hz, 2000 impulse/session, 110% RMT, B-65 figure-8 coil., LDLPFC, 15 session	MDE	Yes (TMS, No = 4; SHAM, No = 8)	0	no
George *et al* [62], 2014	Active TMS, No = 20, age=38.7 ± 15 (M = 18). Sham = 21, age = 46.1 ± 15.9 (M = 17)	Only TMS	rTMS, 10 Hz, 6000 impulse/session, 120% RMT, B-65 figure-8 coil., LDLPFC, 9 session	MDE	Yes (TMS, No = 7; SHAM, No = 6)	0	no

Lingeswaran [51], 2011	Active TMS, No = 9, age = 34 ± 10.5 (M = 3). Sham = 14, age = 37.26 ± 11.8 NS (M = 6)	Only TMS	rTMS, 10 Hz, 500 impulse/session, 100% RMT, B-65 figure-8 coil, LDLPFC, 10 session	MDE	No	0	no
Pallanti *et al* [54], 2010-A	Active TMS, No = 20, age=47.6 ± 12.33, (M = 9). Sham = 20, age = 47.85 ± 9.12 (M = 8)	Only TMS	Bilateral rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65 figure-8 coil., RDLPFC, 15 session AND rTMS, 10 Hz, 1000 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 15 session	TRD	No (light and not worth mentioning)	0	no
Pallanti *et al* [54], 2010-B	Active TMS, No = 20, age = 51.2 ± 12.33, (M = 8). Sham = 20, age = 47.85 ± 9.12 (M = 8)	TMS + placebo	rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65 figure-8 coil., RDLPFC, 15 session	TRD	No (light and not worth mentioning)	0	no
Fitzgerald[55], 2008	Active TMS, No = 30, age = 45.7 ± 10.8 (M = 10). Sham = 28, age = 44.8 ± 11.4 (M = 15)	Only TMS	LF rTMS, 1 Hz, 900 impulse/session, 110% RMT, B-65 figure-8 coil., rDLPFC, 10 session	Depression NS	No (light and not worth mentioning)	0	no
Fitzgerald *et al* [44], 2007	Active TMS, No = 25, age = 46.8 ± 10.7 (M = 10). Sham = 25, age = 43.7 ± 10.2 (M = 9)	Only TMS	Bilateral rTMS, 10 Hz, 750 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 30 session AND Bilateral rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65 figure-8 coil., RDLPFC, 30 session	TRD	No (light and not worth mentioning)	0	no
O'Reardon *et al*[50], 2007	Active TMS, No = 155, age = 47.9 ± 11 (M = 69). Sham = 146, age = 48.7 ± 10.6 (M = 72)	Only TMS	rTMS, 10 Hz, 3000 impulse/session, 120% NS coil, LDLPFC, 25 session	MDE	No (light and not worth mentioning)	0	no
Fitzgerald *et al* [43], 2006	Active TMS, No = 25, age = 46.8 ± 10.7 (M = 10). Sham = 25, age = 43.7 ± 10.2 (M = 9)	Only TMS	Bilateral rTMS, 10 Hz, 750 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 30 session AND Bilateral rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65figure-8 coil., RDLPFC, 30 session	TRD	No (light and not worth mentioning)	0	no
Rumi *et al*[48], 2005	Active TMS, No = 22, age = 39.3 ± 12.8 (M = 3). Sham = 24, age = 38.9 ± 8.8 (M = 4)	TMS + Amitriptyline	rTMS, 5 Hz, 1250 impulse/session, 120% RMT, B-65 figure-8 coil, LDLPFC, 20 session	MDE	No (light and not worth mentioning)	0	no
Boggio *et al* [49], 2005	Active TMS, No = NS, age = NS (M = NS). Sham = NS, age = NS, (M = NS)	TMS + fluoxetine+ placebo	rTMS, 15 Hz, 3000 impulse/session, 110% RMT, B-65figure-8 coil, LDLPFC, 10 session	MDE in Parkinson's disease	No	0	0
Poulet *et al* [46], 2004	Active TMS, No = NS, age=NS (M = NS). Sham = NS, age = NS (M = NS)	TMS + paroxetine	rTMS, 10 Hz, 400 impulse/session, 80% RMT, B-65 figure-8 coil, LDLPFC, 10 session	MDE	No	0	no
Mosimann *et al* [47], 2004	Active TMS, No = 15, age = 60 ± 13.4 (M = 10). Sham = 9, age = 64.4 ± 13 (M = 5)	Only TMS	rTMS, 20 Hz, 1600 impulse/session, 100% RMT, B-65 figure-8 coil, LDLPFC, 10 session	MDE	Yes (TMS, No = 7; SHAM, No = 5)	1	no
Hansen *et al* [45], 2004	Active TMS, No = 6, age = 42.5 (M = 4). Sham = 7, age = 46, (M = 5)	TMS + antidepressant	rTMS, 10 Hz, 2000 impulse/session, 90% RMT, B-65 figure-8 coil, LDLPFC, 10 session	MDE	No	0	no
Nahas *et al* [41], 2003	Active TMS, No = 11, age = 42.4 ± 7.3 (M = 4). Sham = 12, age = 43.4 ± 9.3 (M = 5)	Only TMS	rTMS, 5 Hz, 1600 impulse/session, 110% RMT, B-65 figure-8 coil, LDLPFC, 10 session	BD	No (light and not worth mentioning)		no
Fitzgerald *et al* [66], 2003-A	Active TMS, No = 20, age = 42.4 ± 9.8 (M = 12). Sham = 20, age = 49C.15 ± 14.243 (M = 9)	Only TMS	rTMS, 1 Hz, 300 impulse/session, 100% RMT, B-65 figure-8 coil, RDLPFC, 10 session	BD,MDE, TRD	No (light and not worth mentioning)	0	no
Fitzgerald *et al* [66], 2003-B	Active TMS, No = 20, age = 45.55 ± 11.49 (M = 13). Sham = 20, age = 49.15 ± 14.243 (M = 9)	Only TMS	rTMS, 10 Hz, 1000 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 10 session	BD,MDE, TRD	No (light and not worth mentioning)	1	no

Pascual-Leone *et al*[60], 1996	Active TMS, No = 17, age = 48.6 ± NS (M = 6). Sham = 17, age = 48.6 ± NS (M = 6)	Only TMS	rTMS, 10 Hz, 2000 impulse/session, 90% RMT, B-65 figure-8 coil, LDLPFC, 5 session	Psychotic depression	Yes (TMS, No = 7; SHAM, No = 7)	0	no

SD: Standard deviation; RMT: Resting motor thresholds; HMS: Hypomanic/manic switch; TMS: Transcranial magnetic stimulation; rTMS: Repetitive TMS; RDLPFC: Right dorsolateral prefrontal cortex; LDLPFC: Left dorsolateral prefrontal cortex; TRD: Treatment resistant depression; MDE: Major depressive episode; dTMS: Deep TMS; piTBS: Prolonged intermittent theta burst stimulation; iTBS: Intermittent theta-burst stimulation; BD: Bipolar depression; MDD: Major depressive disorder.

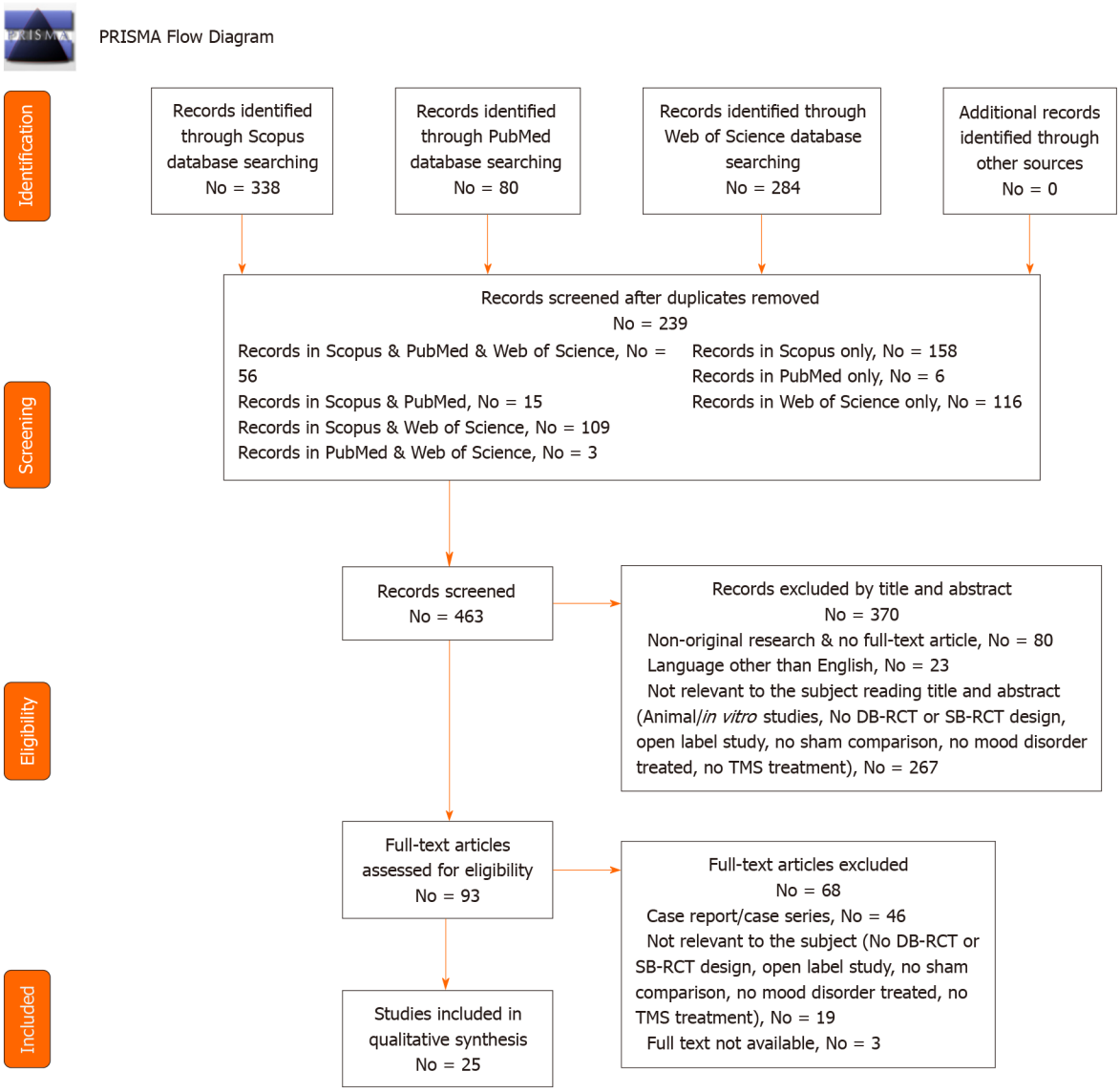


Figure 1 PRISMA flow diagram: Studies included in qualitative and quantitative synthesis. DB-RCT: Double blind randomized controlled trials; SB-RCT: Single blind randomized controlled trials.

treatment at 1 Hz (No = 7)[44,53-55,61,63,65] and those who have used a HF treatment (No = 21) divided in 5 Hz (No = 2)[41,48], 10 Hz (No = 15)[42-46,50,51,53-55,57,59,60,62,63], 15 Hz (No = 1)[49] and 20 Hz (No = 1)[47].

The number of pulses/session was very heterogeneous, more frequently 2000 pulses/session (No = 3)[42,45,60] and 3000 pulses/session (No = 2)[49,50].

Side effects

Only eight studies reported at least one side effect[42,47,53,59,60,62,63]. HMSs (described as greater energy, insomnia, irritability, anxiety and suicidal attempt in bipolar patients), were present in four studies[44,47,52,53] and, in particular, once in the sham group and three times in the active group. Only one episode of HMS was

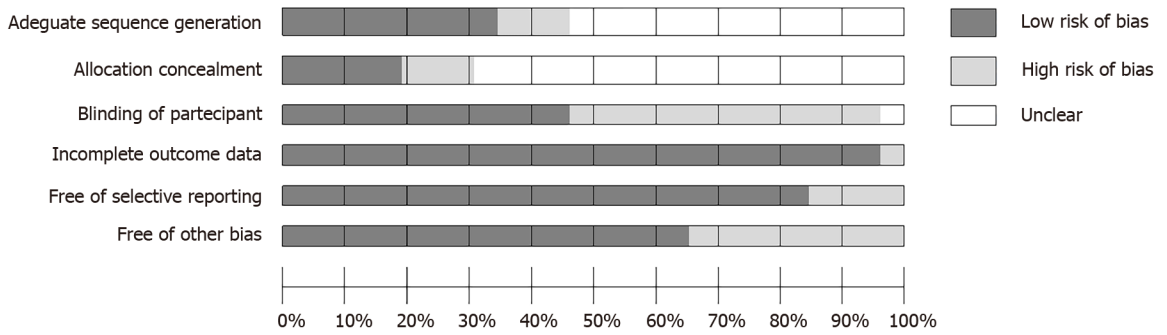


Figure 2 Risk of bias assessment.

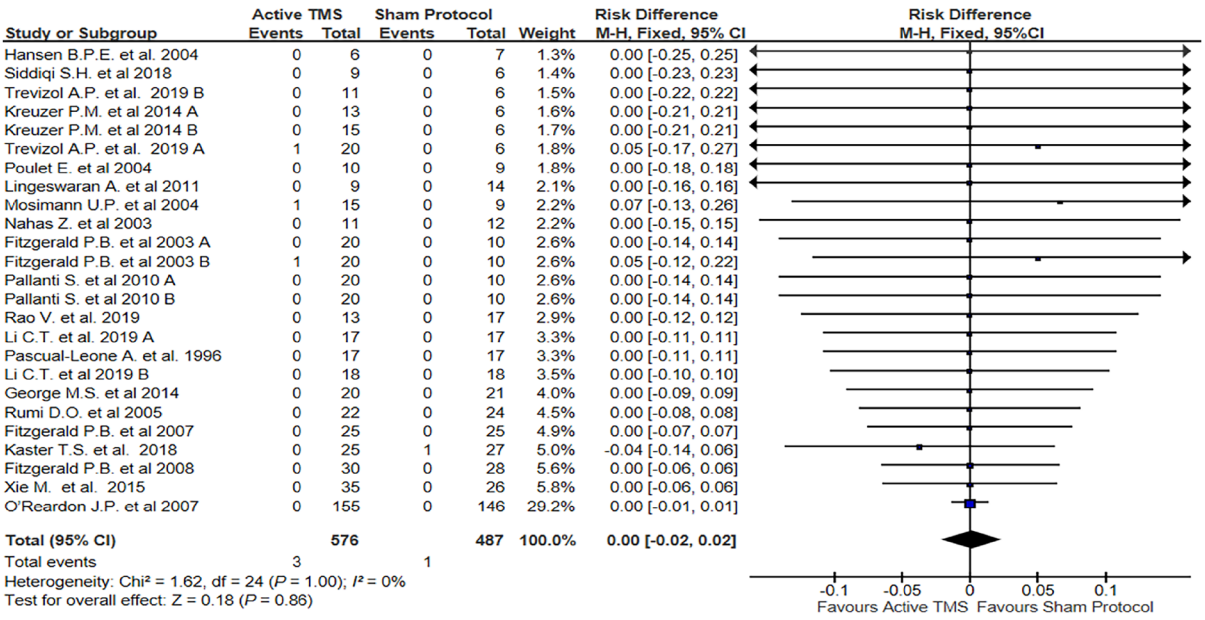


Figure 3 Forest plot: Risk to develop a hypomanic/manic switch after a transcranial magnetic stimulation protocol. TMS: Transcranial magnetic stimulation.

specifically reported[66], after stopping taking a mood stabilizer and after the end of the rTMS treatment. No drop-outs due to HMSs were reported. None of the studies that used antidepressants in addition to TMS treatment reported the onset of HMS[45,46,48,49].

Risk of bias

The results of the risk of bias assessment reveal a good quality of the reported data, as evidenced by the items "*Incomplete Outcome Data*" and "*Free of Selective Report*". However, only a few of the included studies accurately indicated the blinding method and the allocation concealment (Figure 2).

Meta-analysis of rTMS protocols

The meta-analysis of the 25 studies included (No. of subjects involved in active stimulation = 576; No. of subjects involved in sham protocol = 487), showed no significant results about the risk of developing HMS after TMS stimulation (RD = 0.00; 95%CI = -0.02-0.02; P = 1.00; I^2 = 0%) for a fixed effect.

The inspection of the funnel plot of the RD of the included studies (Fixed Effect) suggested a symmetry of the studies, showing the same concentration of studies on the left and on the right of the mean RD (Figure 4).

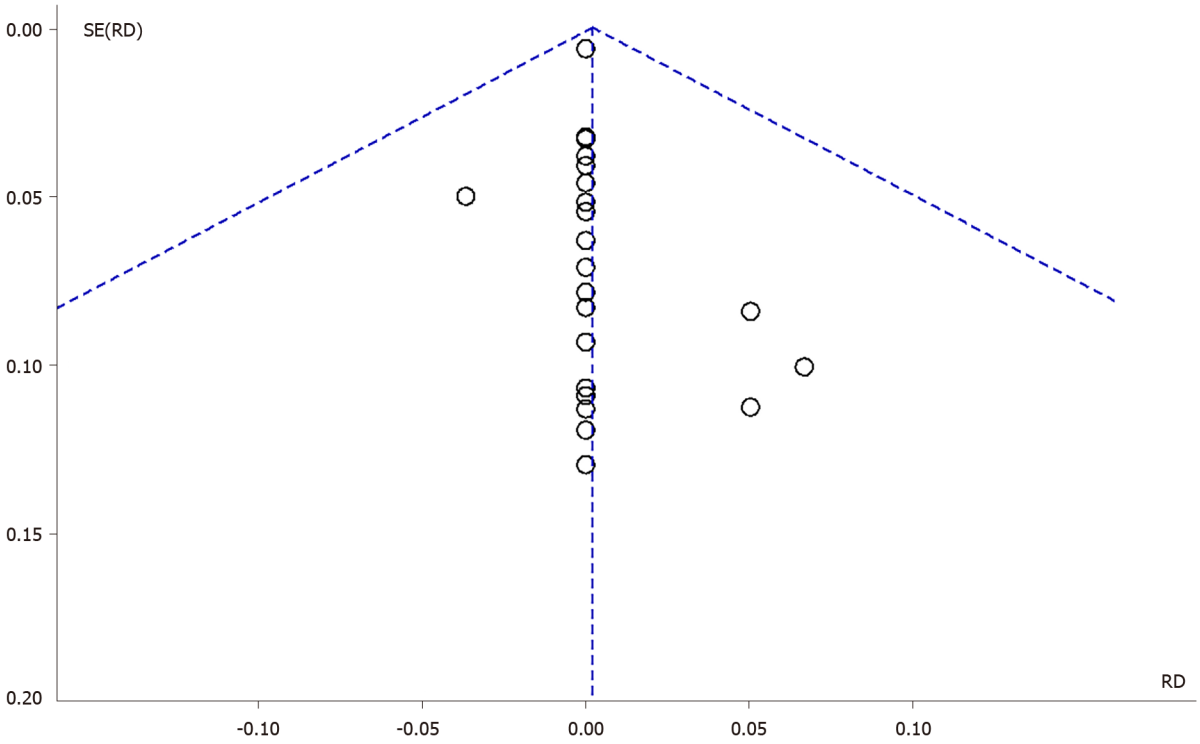


Figure 4 Funnel plot for publication bias. RD: Risk difference.

DISCUSSION

The mechanisms underlying HMSs in mood disorders are complex and still unknown, even if a main role of increased levels of dopamine and/or norepinephrine and of seasonal changes of neural activity were suggested[67]. Antidepressant treatments are well known triggers for HMSs, especially in bipolar disorders[68]. Due to its increasing use in the treatment of mood disorders, the same concern has been voiced about the safety of TMS. In particular, in a previous meta-analysis on the topic, it was hypothesized that HMS was induced by a too intensive treatment with TMS and an incorrect diagnosis of unipolar depression[69]. However, the most recent scientific literature regarding the use of TMS in mood disorders seems to deny the hypomanic effect of TMS. Nowadays, in fact, several TMS treatments (rTMS and TBS in particular) [6,70] are increasingly used not only for the therapy of TRD but also for the treatment of mood disorders in general, including bipolar disorders[71]. However, a critical role on the onset of HMS is probably played by the concomitant use of high-dosage antidepressant treatments[72,73], pointing out the importance of a deep and accurate anamnesis.

In our systematic review focused on RCTs using TMS to treat mood disorders, we found that only 4/25 studies reported a HMS as an adverse event, and the difference between sham and active treatment was not significant.

The most used protocol was rTMS, set at 10 Hz (16/25 studies), 120% RTM (9/25 studies) with a variable number of pulses (the most common included the 2,000 pulses/session present in 3/26 studies). The most investigated brain area was the DLPFC, (24/25 studies); only one study examined the AC with a deep-brain stimulation technique. However, in the context of the DLPFC, lateralization to the right seems preferred in the context of a LF stimulation (all eight studies in question stimulate the RDLPFC) while the left one in the context of a HF (all of the remaining 17 studies stimulate the LDLPFC). The application of the most widely used research protocols could therefore be a useful method to avoid the genesis of HMSs.

Another aspect highlighted by our results is the absence of drop-outs due to HMS. Considering the severity of HMS symptomatology, the absence of drop-outs is a further indication of the TMS safety in the treatment of MD.

CONCLUSION

Considering the still not understood and complex mechanisms underlying the development of HMS, from the results of our systematic review of the literature and from our meta-analysis (although in the context of a statistical non-significance), it seems clear that by applying the most usual protocols of rTMS and TBS and applying, where necessary, the appropriate precautionary measures (for example going on with mood stabilizers) TMS can be considered a safe technique also in the context of mood disorders.

ARTICLE HIGHLIGHTS

Research background

One of the most innovative and most investigated non-invasive brain stimulation techniques is Transcranial Magnetic Stimulation (TMS). This device has received Food and Drug Administration approval for the treatment of various neurological (headache) and psychiatric (treatment resistant depression) disorders. Several studies have been conducted to find new applications of TMS in conditions that do not respond or partially respond to standard psychopharmacological therapies.

Research motivation

TMS is an increasingly used technique in the neurological and psychiatric fields. One of the greatest concerns about its use is the possibility of developing severe side effects such as hypomanic/manic switches (HMS).

Research objectives

The aim of this meta-analysis is to quantify the risk of developing HMS after treatment with TMS in mood disorders and to evaluate the drop-out rate due to that adverse event.

Research methods

The search was conducted using PubMed, Scopus and Web of Science databases on March 22, 2020. All procedures were registered on PROSPERO and performed according to the PRISMA guidelines. Only double blind/single blind articles, written in English were included. RevMan 5.4 Software for Windows was used to perform the meta-analysis.

Research results

Of the 25 eligible studies, only four HMSs were described. No dropouts were reported due to symptoms severity.

Research conclusions

Our data confirm that, by applying appropriate psychopharmacological and anamnestic precautions, TMS is a safe technique for treating mood disorders.

Research perspectives

Greater uniformity of protocols, their online registration and the timely reporting of side effects on scientific papers could guarantee a more accurate analysis of the health risks induced by TMS in future meta-analyses.

ACKNOWLEDGEMENTS

We would like to thank Alessia Di Ferdinando for kindly reviewing the language and Gianluca Mancusi for his precious help in the revision of references.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 August 19; 11(8): 491-506

DOI: 10.5498/wjp.v11.i8.491

ISSN 2220-3206 (online)

SCIENTOMETRICS

Knowledge domain and emerging trends in visual hallucination research: A scientometric analysis

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Author contributions: Zhong M wrote the paper; Wu Z, Jiang X, and Shen B downloaded and analyzed the data; Zhang L and Zhu J designed the study.

Supported by National Key Research and Development Program of China, No. 2016YFC1306601; Special Funds of the Jiangsu Provincial Key Research and Development Program, No. BE2018610 and No. BE2019612; Jiangsu Provincial Cadre Health Projects, No. BJ16001 and No. BJ17006; Special Funds of the Jiangsu Provincial 333 High-level Talent Cultivation Projects; and Nanjing Medical Science and Technology Development Foundation, No. ZKX17031 and No. QRX17026.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Visual hallucination (VH) refers to a spontaneous visual perception without corresponding external stimuli and often occurs in ophthalmological and neuropsychiatric disorders. It is associated with poor quality of life, and increased patient hospitalization and nursing home admission. To date, a scientometric analysis of research on VH is lacking.

AIM

To objectively summarize the features of VH research and gain insights into the emerging trends in research on VH.

METHODS

CiteSpace V was used in this article. Publication outputs, document types, geographic distributions, co-authorship status, research hotspots, and co-citation status were analyzed. A total of 2176 original articles and 465 reviews were included in the database downloaded from the Web of Science Core Collection. We selected the top 50 most cited or occurring articles or items to create a visualized network with a 1-year interval. In the document co-citation analysis stage, we performed clustering analysis on co-cited references, and log likelihood tests were used to name the clusters.

RESULTS

The results showed that most publications can be classified into neurology, sports, and ophthalmology studies. In addition, North America, Europe, Asia and Australia published the most documents. Some well-known authors have always had a leading role in this field; meanwhile, new authors keep emerging. A relatively stable cooperation has been formed among many authors. Furthermore,

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: November 29, 2020
Peer-review started: November 29, 2020
First decision: March 16, 2021
Revised: March 29, 2021
Accepted: July 5, 2021
Article in press: July 5, 2021
Published online: August 19, 2021

P-Reviewer: Shiina A
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Wang LYT

neuropsychiatric symptom and functional connectivity are the top hotspots. Research on VH in dementia with Lewy bodies and Parkinson's disease (PD) have received much attention. Studies on VH in PD are likely to be the new emerging trends in the future, especially the mechanisms of VH.

CONCLUSION
Research on VH has formed a complete system. More large-scale clinical and in-depth basic research are required to better understand the mechanisms underlying VH, which will contribute to our understanding of the patho-physiology and therapeutic options for VH.

Key Words: Visual hallucination; Psychiatry; Parkinson's disease; Dementia with Lewy bodies; CiteSpace; Scientometric

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Core Tip: Visual hallucination (VH) is very common and research on VH keeps emerging. In this review, CiteSpace V was used to objectively summarize the features of VH research and gain insights into the emerging trends for research on VH. Publication outputs, document types, geographic distributions, co-authorship status, research hotspots, and co-citation status were analyzed.

Citation: Zhong M, Wu Z, Jiang X, Shen B, Zhu J, Zhang L. Knowledge domain and emerging trends in visual hallucination research: A scientometric analysis. *World J Psychiatr* 2021; 11(8): 491-506
URL: https://www.wjgnet.com/2220-3206/full/v11/i8/491.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i8.491

INTRODUCTION

Visual hallucination (VH) is a spontaneous visual perception in the absence of corresponding external stimuli; it has been aptly described by Collerton *et al*[1] as seeing things that are not there. It is a common symptom often associated with eye diseases (*e.g.*, Charles Bonnet syndrome [CBS])[2,3] and neuropsychiatric conditions (*e.g.*, Parkinson's disease [PD][4-6], dementia with Lewy bodies [DLB][7-9], epilepsy[10], schizophrenia[11,12], occipital stroke[13]). In some cases, it can be a side effect of medications, such as anticholinergics, dopamine agonists, and a wide range of medications modulating diverse neurochemical pathways[14]. VH is related to the poisoning and withdrawal of alcohol, cannabis, and cocaine and other physical conditions such as physical illness and stress[15-17]. A small percentage of healthy individuals have reported experienced VH in their life[18,19]. Although VH occurs in a significant proportion of cases, it mostly occurs sporadically in healthy people. The frequent occurrence of VH tends to be a signal of pathology[20].

The prevalence of VH varies widely in different diseases. Almost 40% of people with eye or visual pathway disease, typically macular degeneration, develop VH known as CBS[3]. VH is also a core feature for DLB diagnosis and has a 54%-70% prevalence in DLB[21,22]. Furthermore, 22%-78% of patients with PD suffer from VH [23]. Hallucinations have been described as a hallmark of schizophrenia, showing a prevalence of 36.5%[24]. The lifetime prevalence of VH in healthy subjects is 3.4%[25]. Progressive and recurrent VH is often associated with a likelihood of poor life quality, increased patient hospitalization, and nursing home admission[26,27]. In addition, it is a risk factor for dementia and is associated with the high mortality rate of patients with dementia[28,29].

Extensive research on VH has been widely conducted worldwide, and a large number of papers have been published. However, to the best of our knowledge, VH has not been systematically reviewed by scientometric analysis. The knowledge domain and emerging trends of existing research have not been fully understood. Therefore, objectively summarizing the features of VH and gaining insights into the new emerging trends for research on VH are crucial. This work conducted a systematic

and scientific analysis of the research on VH by using CiteSpace, a powerful tool for data analysis and visualization[30]. The findings elaborate on annual publications, document type, co-country, co-authorship, burst keywords, and document co-citation.

MATERIALS AND METHODS

Data collection

Our data were retrieved from the Web of Science Core Collection (WOSCC), which is the specified article data source for CiteSpace as it contains citation information. An initial topic search for 'visual hallucination' resulted in 3178 records published between 1985 and 2020. We filtered out conference abstracts and proceedings and corrigendum documents, which were less representative[31]. We believe that original research papers can better represent the state of the research field compared with other types of documents. Review papers can attach additional importance to the representative papers selected by domain experts[32]. A total of 2641 publications which consist of 2176 articles and 465 reviews, were selected as a database to be used in subsequent analysis (537 were excluded). Then we downloaded raw data, which included full records and cited references, from WOSCC in the form of plain text files.

Statistical methods

CiteSpace V based on Java was utilized for information visualization analysis, which provides insights into VH research and makes it easy to effectively follow the progress of information[30,32,33]. In this study, we selected the top 50 most cited or occurring articles or items to create a visualized network with a 1-year interval. In the document co-citation analysis stage, we performed clustering analysis on co-cited references, in which similar references were combined to determine related research fields. Moreover, log likelihood tests (LLRs) typically provide the unique and best results that consider all of the contents of a cluster; thus, we extracted noun phrases from the keywords of articles that cited a cluster on the basis of LLR to characterize the nature of the cluster[34]. Office Excel 2019 was also applied to our study.

RESULTS

Characters of publication outputs

To determine the general trend of VH research, we summarized the publications of original articles and reviews over the years. The earliest record we found in WOSCC was published in 1999. The results in Figure 1 show that the publication outputs are mainly in a fluctuating growth trend, with an increase from 61 in 1999 to 182 in 2020.

Analysis of document type

Dual-map overlays in CiteSpace can help reveal the trends of the scientific portfolio under a background of a global map of scientific literature. The background has two base maps, the left part shows a base map of citing journals and the right part shows the cited journals, each containing a network of over 10000 journals. Similar journals form a cluster, which is labeled on the basis of the terms in the journal titles of the cluster. The reference relationships between the left and right parts are connected by colored curves that indicate how a current research obtains inspiration from previous works[33]. The vertical and horizontal axes of the ellipse in the left part respectively indicate the number of articles and authors published in journals. The number of citations determines the size of the ellipse in the right part[34]. Figure 2 shows a dual-map overlay visualization of the citing and cited papers with regard to the topic search on VH. Four threads of citations stand out. They originate from four clusters in the citing base map: the orange threads from the cluster of molecular, biology and immunology, the pink threads from the cluster of neurology sports and ophthalmology, the blue threads from the cluster of psychology, education and health, and the green threads from the cluster of medicine, medical and clinical. These threads generally point to two clusters in the cited base map. One is the cluster of molecular, biology and genetics; the other is the cluster of psychology, education and social. New developments are highlighted in red from the publication point of view. The new progression of VH is in the field of mathematics, systems and mathematical, which is worth further research.

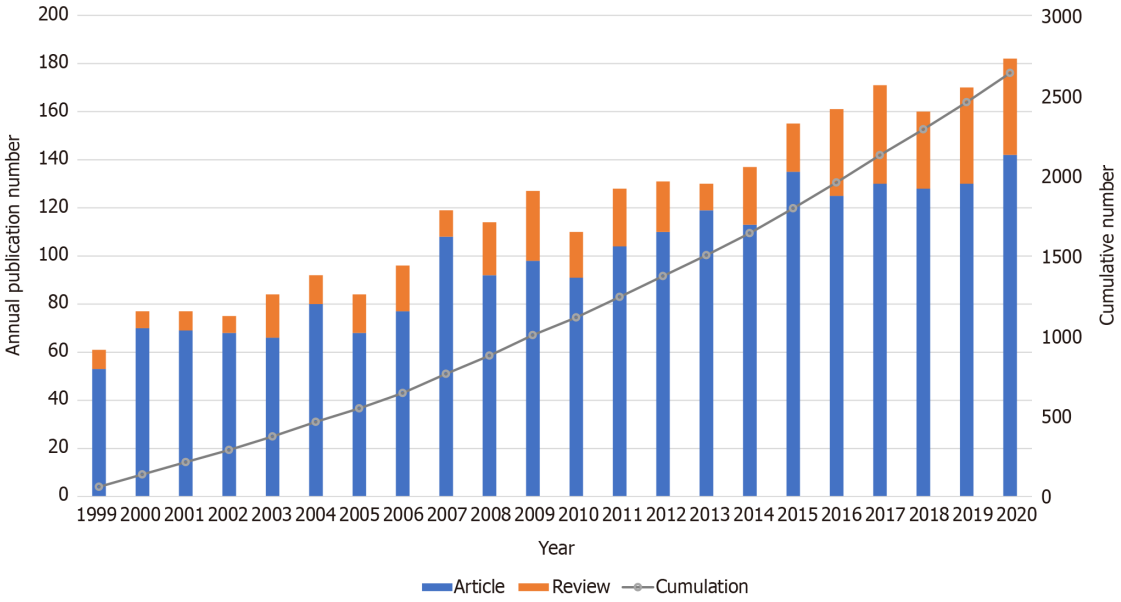


Figure 1 Publication output performance during 1999-2020.

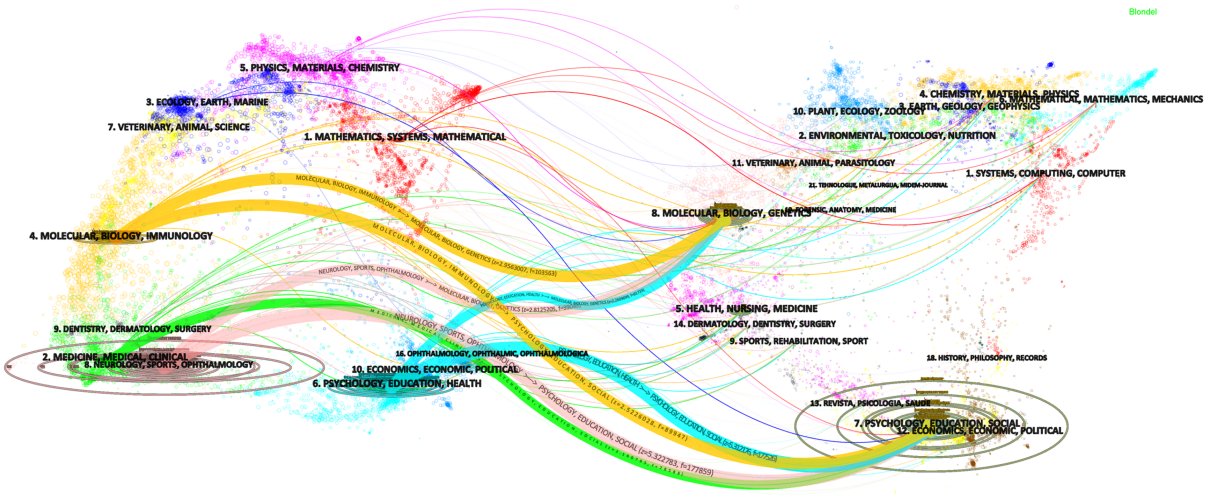


Figure 2 Dual-map overlay for final document storage. The nature of each region is labeled by the journal of the corresponding region. The colored curve represents the reference path from the citing base map on the left to the cited base map on the right. The number of articles and authors published in journals determines the size of the ellipse in the graph.

Geographic distribution of the publications

The total number of publications by country was analyzed to understand their geographic distribution. We checked the names of all countries and merged some regions into corresponding countries. The analysis is presented in Figure 3. The larger the published quantity, the deeper the color. The United States, England, and Japan were the top three countries.

Distribution of authors and co-authorship

Co-authorship was analyzed to detect active authors and their cooperation in the field. For accuracy and objectivity, we reviewed all of the authors' names to reduce misidentification. The result is displayed in Figure 4. The font size of each author's name corresponds to the number of articles by each author, which represents the contribution of the author to this field. The color of the tree ring stands for the year in which the author published his or her articles. The thickness of the tree ring represents the number of his or her articles in a particular year. Collaborative intensity between authors is indicated by the thickness of a connecting line. Chronological order information is included in the color of the lines that appear together between nodes:

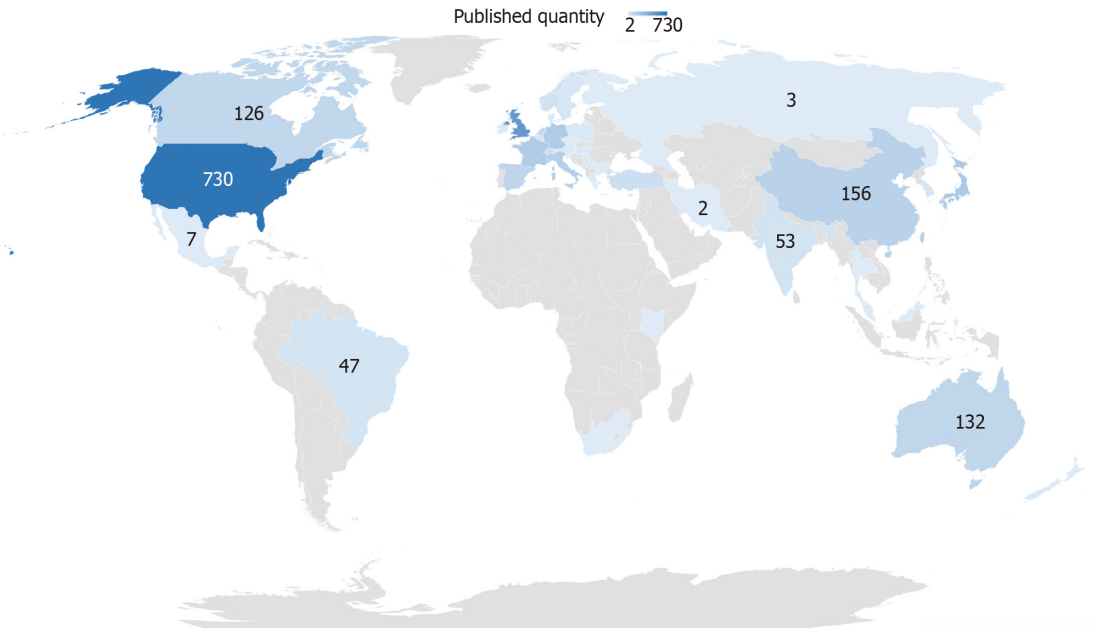


Figure 3 Geographic distribution of the countries. The figures represent the corresponding country's total published quantity on visual hallucination between 1999 and 2020. The larger the published quantity, the deeper the color.

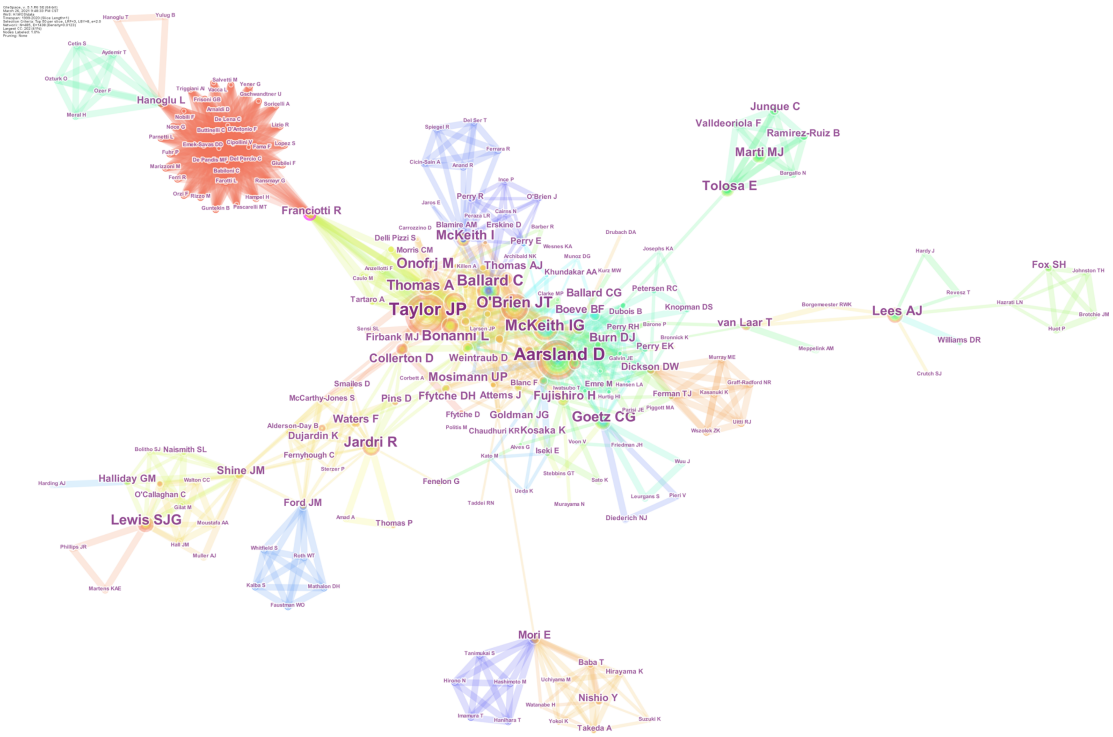


Figure 4 Map of active authors in the visual hallucination field. The font size of each author's name represents the article counts of each author. Different colors inside the circle represent different time intervals. The collaborative intensity between authors can be seen from the thickness of the connecting line.

blue represents the oldest, green the middle, and red the newest. In summary, top-productivity authors have greatly contributed to this field, and a relatively stable cooperation has formed among many authors. More than 485 authors have made contributions to the research on VH. Among these authors, Taylor JP (40 articles) ranked first, followed by Aarsland D (38 articles), O'Brien JT (25 articles) and McKeith IG (24 articles).

Keywords burst detection

The topics involved in VH can be described by the keywords extracted from each

article in the dataset[31]; however, new insights into this field should be determined. The burst patterns of keywords reveal research hotspots in the field of VH because a burst of a keyword is a sharp increase of the keyword that is likely to have a great influence[32]. Among the 340 selected keywords, 104 have the strongest strength of burst during 1999-2020. Figure 5 lists the top 104 keywords with strongest burst. The blue line represents the timeline from 1999 to 2020, and the red line stands for the years when a keyword has burst. Among the top 104 keywords, particular attention was paid to those keywords that remain to have a burst until 2020, such as 'neuropsychiatric symptom' and 'functional connectivity'. Other burst keywords included 'auditory verbal hallucination, diagnostic criteria, functional magnetic resonance imaging (fMRI), meta-analysis, management, impulse control disorder, sleep behavior disorder, and default mode network'.

Analysis of co-cited references

The most outstanding function in CiteSpace is co-citation analysis, which was used to analyze all references of the 2641 documents downloaded from WOSCC, and the top 50 most-cited references each year was select. As a result, 776 nodes of references were generated and automatically linked in the visual interface. Only if two references were cited by the same document could they be connected. If two references were often cited by documents together, they tended to have a close relationship, so they were classified to the same cluster. In our analysis, the smallest clusters were filed out, and 69 clusters were left. The information on all references formed the intellectual base of this field, and 776 highly cited references were classic documents[32]. By mining the most classic references in each cluster, we can understand the general development process and research frontiers of the VH research field. An overview of a co-cited reference network is shown in Figure 6. The overall structure can be divided into three major parts: the upper left part of the nodes and links, which represent the co-citation of the first 7 years from 1999 to 2005, is essentially in blue. The central part of the network is mainly in green and yellow, which indicates that the relationship was probably constructed between 2006 and 2012. The bottom right part is predominantly in red, and connections are formed credibly in the most recent 8 years.

The quantity of the clusters can be measured *via* two indexes: Modularity Q value and Silhouettre value. Modularity Q value is a network modularization index with a value range of 0-1. $Q > 0.3$ indicates that the structure of a certain cluster is significant. Silhouettre value indicates the homogeneity or consistency of the cluster. The closer the S value is to 1, the better the homogeneity of the cluster is. When $S > 0.5$, the clustering result can be considered reasonable; when $S > 0.7$, the clustering result is efficient. The number of references constituting the cluster must be greater than 10 [35]. Table 1 lists the major clusters of co-cited references selected from 69 clusters. In general, the 10 clusters in the table represent 10 research directions in the field.

The earliest formed cluster is Cluster #1 senile dementia, whose average publication year is 1997. It has more than 100 references as its members. A common theme of this cluster is identifying DLB from Alzheimer's disease, which are both belong to senile dementia[36-38]. The 82 members of Cluster #2 are evenly published in 2001, mainly involve PD with hallucination and focus on phenomenology[39]. Cluster #5 Charles bonnet syndrome, #3 incident dementia, and #6 schizophrenia introduce CBS, DLB and schizophrenia, respectively. These diseases all have VH as a hallmark. The research foundation in the three fields was mostly established in 2001, 2005, and 2014. Their high silhouette values indicate a high homogeneity of the clusters. Importantly, Cluster #2 and #3 are very close to each other in Figure 6; this may be partly because both PD and DLB are Lewy bodies (LB) diseases[40], and persistent VH is related to the spread of LBs[29].

The largest cluster is Cluster #0 labeled body disease, which includes 154 complete references. These references' average publication year is 2011. Cluster #4 Parkinson's disease dementia (PDD), which has 70 group members with an average publication year of 2014. These two clusters constitute the main body of VH research in the last decade and are closely connected in Figure 6 because they include research that introduces PD with VH. Cluster #0 focuses on the evidence of changes in brain structure and function in PD with VH[41,42], while Cluster #4 is mainly about the comparison and management of VH in PDD and DLB[43,44].

Other clusters, such as Cluster #7 impulse control disorder and Cluster #9 REM sleep behavior disorder (RBD) are formed more recently. Impulse control disorder and RBD are both included in the non-motor symptoms of PD. The co-cited references in these two clusters demonstrate the relationship between these two symptoms and VH respectively. Cluster #10 5-HT2A involves the investigation of serotonin 2A receptor in PD with psychosis (PDP)[45,46]. It includes publications averagely in 2010.

Table 1 Major clusters of co-cited references

Cluster	Size	Silhouette	Mean (year)	Label (LLR)
0	154	0.727	2011	Body disease
1	110	0.883	1997	Senile dementia
2	82	0.715	2001	Hallucinosis
3	71	0.77	2005	Incident dementia
4	70	0.903	2014	Parkinson's disease dementia
5	57	0.957	2001	Charles bonnet syndrome
6	52	0.968	2014	Schizophrenia
7	47	0.822	2008	Impulse control disorder
9	11	0.975	2006	Rem sleep behavior disorder
10	11	0.99	2010	5 HT2a receptor

Ten major clusters were selected from the total 69 clusters. Each cluster represents a research subfield. The size is the number of cited articles in one cluster. The Silhouettre value indicates the homogeneity or consistency of the cluster. Mean year stands for the mean publication year of the cited articles. The label of cluster is based on log-likelihood ratio.

To detect emerging trends in the field, we further investigated the top high-quality co-cited references. In this part, we used the first author's name plus the publication year as a notion to refer to the articles extracted from 776 co-cited articles. Top three references are shown in Table 2 as ranked by citation counts, centrality, burst and sigma respectively.

DISCUSSION

Research on VH has formed a complete system. A total of 2641 articles were published between 1999 and 2020. Apparently, more original articles than reviews were published every year. In terms of the cumulative number of publications, the cumulation in 2020 (2641) is approximately twice that in 2011 (1244). Following the analysis of the chart, we can predict that this study period will further attract attention and continually grow in the next few years.

On a global scale, many countries conduct numerous studies on VH. This field has attracted wide attention worldwide. However, research imbalance between countries exists. To date, studies on VH have been predominantly conducted in North America (*e.g.*, United States and Canada), Europe (*e.g.*, United Kingdom, France, Germany), Asia (*e.g.*, Japan and China), and Australia. The United States published the largest number of studies between 1999 and 2020. England was the second country that stands out in studies involving VH.

Dr. Taylor JP and Dr. Aarsland D are pioneers in the field. Dr. Taylor JP pushes back the frontiers of DLB[47] and plays an important role in the studies on the visual cortical excitability in the VH of DLB[7,48-50]. Dr. Aarsland D opens doors to reveal the psychiatric symptoms of PD[51-54]; his outstanding contribution to this field is clarifying that the presence of hallucination in PD is an important contributor to institutionalization and caregiver distress[55,56]. In addition, a group of new experts has emerged in this field in 2020, and their cooperation is very close. The team is mainly engaged in the research of electroencephalogram and evoked potentials of VHs, which is a new research breakthrough[57,58].

The most active topics of this field are 'neuropsychiatric symptom' and 'functional connectivity'. For example, the burst period of keywords 'neuropsychiatric symptom' is from 2014 to 2020, and the burst intensity is 11.91. Cross-diseases (mainly psychiatric and neurological diseases) VH research started in 2014[59]. This article sparked a heated discussion on the relationship between VH in psychiatric and neurological diseases. Many scholars tend to believe that VH in different neuropsychiatry disorders have the same mechanism. Some experts have proposed that impairments in attentional network activity can explain all hallucinations in various diseases[60]. Yao *et al*[61] proposed that apart from schizophrenia, aberrant default mode network (DMN) was also found to contribute to the VH in PD. Meanwhile, the dorsal attention

Table 2 Top three references ranked by four values respectively

Values		Ref.	Journal, volume, start page	Cluster #
Counts	124	Mckeith *et al*[69], 2005	*Neurology*, 65, 1863	3
	93	Harding *et al*[70], 2002	*Brain*, 125, 391	3
	91	Mckeith *et al*[36], 1996	*Neurology*, 47, 1113	1
Centrality	0.09	Aarsland *et al*[71], 2002	*J Neurol Neurosur Ps*, 72, 708	1
	0.08	Goetz *et al*[72], 2011	*Movement Disord*, 26, 2196	0
	0.07	Cummings *et al*[46], 2014	*Lancet*, 383, 533	0
Bursts	44.12	Mckeith *et al*[74], 2017	*Neurology*, 89, 88	4
	43.96	Mckeith *et al*[36], 1996	*Neurology*, 47, 1113	1
	43.86	Mckeith *et al*[69], 2005	*Neurology*, 65, 1863	3
Sigma	4.49	Teunisse *et al*[79], 1996,	*Lancet*, 347, 794	5
	4.36	Cummings *et al*[46], 2014	*Lancet*, 383, 533	0
	4.04	Mckeith *et al*[69], 2005	*Neurology*, 65, 1863	3

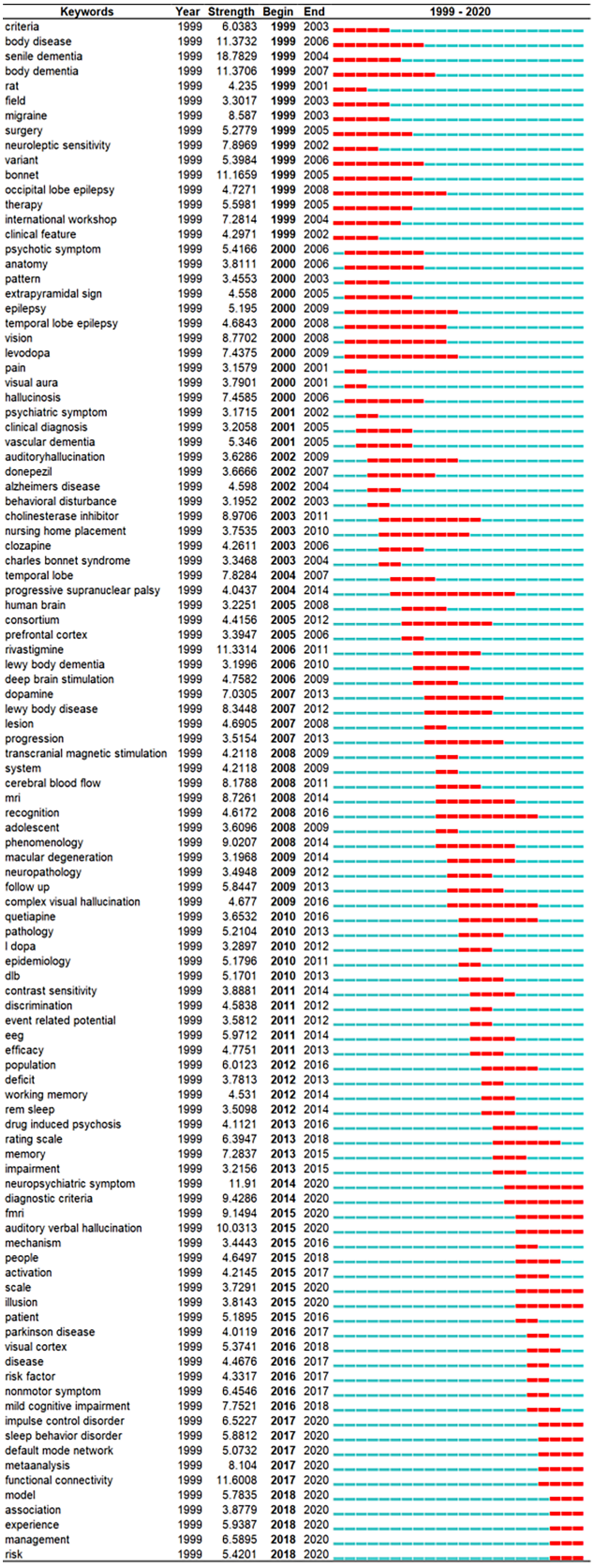
network (DAN) and the ventral attention network (VAN) also play important roles in the occurrence of VH[62]. DMN involves the function of sensory information perception and processing, while VAN engages attention to salient stimuli and DAN generates selective attention. The underactivation of VAN and overactivation of DAN and DMN lead to the recall of previously stored perception information, resulting in VH[63]. In the cohort of patients with VH, thinner retinal nerve fiber layer thickness was found by using spectral domain optical coherence tomography[64], and grey matter atrophy in visual perception region was shown in structural magnetic resonance imaging. These all provide evidence to support the attention deficit network model.

The keyword 'functional connectivity' burst from 2017 to 2020 with a burst intensity of 11.6008. Although current research has produced deep insights into the symptoms and nature of VH, the pathophysiology and etiology of VH remain unclear. Therefore, understanding neural mechanisms has considerable scientific and clinical significance. Evidence from the autopsy can only reveal changes in VH and not explain the cause of VH[65]. Functional neuroimaging studies are beneficial at capturing spontaneous VH in the neuroimaging scanner and the examination is noninvasive[66]. fMRI can investigate changes in specific parts of the brain rather than gross brain abnormalities [67]. It can reveal alterations in brain connectivity even before structural deficits occur. Resting state and task state are two main types of functional neuroimaging in the studies on VH[66]. The most recent research into the neural underpinnings of VH in schizophrenia concluded that the lateral occipital cortex (LOC) of patients showed increased connection with the frontoparietal task-control network and thalamus in the resting state; however, during task switching, LOC has an increase in interaction with the DMN[68].

Emerging trends of VH were identified based on structural and temporal properties derived from the relevant publications.

Landmark articles

Given the groundbreaking contributions, the most cited articles in the research field are often considered the landmarks[31]. Mckeith IG (2005) and Harding AJ (2002) are at the top of the list. Both of them are in Cluster #3. Mckeith IG (1996) is the third most cited article and belongs to Cluster #1. Notably, Mckeith IG is a pioneer in the field of DLB and has published a series of DLB clinical guidelines in Neurology. Mckeith IG (1996) proposed the first consensus guideline for the clinicopathological diagnosis of DLB[36]. In 2005, Mckeith *et al*[69] published the third revised clinical diagnostic and treatment criteria for DLB, which included management in the criteria for the first time. These two guidelines authoritatively summarized the clinicopathological diagnosis of DLB and showed the direction of DLB treatment at that time. The article by Harding *et al*[70] entitled *Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe* advanced the finding that temporal lobe LB is strikingly associated with VH given the distribution of LB in the brain. This result is a



Keywords	Year	Strength	Begin	End	1999 - 2020
criteria	1999	6.0383	1999	2003	
body disease	1999	11.3732	1999	2006	
senile dementia	1999	18.7829	1999	2004	
body dementia	1999	11.3706	1999	2007	
rat	1999	4.235	1999	2001	
field	1999	3.3017	1999	2003	
migraine	1999	8.587	1999	2003	
surgery	1999	5.2779	1999	2005	
neuroleptic sensitivity	1999	7.8969	1999	2002	
variant	1999	5.3984	1999	2006	
bonnet	1999	11.1659	1999	2005	
occipital lobe epilepsy	1999	4.7271	1999	2008	
therapy	1999	5.5981	1999	2005	
international workshop	1999	7.2814	1999	2004	
clinical feature	1999	4.2971	1999	2002	
psychotic symptom	1999	5.4166	2000	2006	
anatomy	1999	3.8111	2000	2006	
pattern	1999	3.4553	2000	2003	
extrapyramidal sign	1999	4.558	2000	2005	
epilepsy	1999	5.195	2000	2009	
temporal lobe epilepsy	1999	4.6843	2000	2008	
vision	1999	8.7702	2000	2008	
levodopa	1999	7.4375	2000	2009	
pain	1999	3.1579	2000	2001	
visual aura	1999	3.7901	2000	2001	
hallucinosis	1999	7.4585	2000	2006	
psychiatric symptom	1999	3.1715	2001	2002	
clinical diagnosis	1999	3.2058	2001	2005	
vascular dementia	1999	5.346	2001	2005	
auditoryhallucination	1999	3.6286	2002	2009	
donepezil	1999	3.6666	2002	2007	
alzheimers disease	1999	4.598	2002	2004	
behavioral disturbance	1999	3.1952	2002	2003	
cholinesterase inhibitor	1999	8.9706	2003	2011	
nursing home placement	1999	3.7535	2003	2010	
clozapine	1999	4.2611	2003	2006	
charles bonnet syndrome	1999	3.3468	2003	2004	
temporal lobe	1999	7.8284	2004	2007	
progressive supranuclear palsy	1999	4.0437	2004	2014	
human brain	1999	3.2251	2005	2008	
consortium	1999	4.4156	2005	2012	
prefrontal cortex	1999	3.3947	2005	2006	
rivastigmine	1999	11.3314	2006	2011	
lewy body dementia	1999	3.1996	2006	2010	
deep brain stimulation	1999	4.7582	2006	2009	
dopamine	1999	7.0305	2007	2013	
lewy body disease	1999	8.3448	2007	2012	
lesion	1999	4.6905	2007	2008	
progression	1999	3.5154	2007	2013	
transcranial magnetic stimulation	1999	4.2118	2008	2009	
system	1999	4.2118	2008	2009	
cerebral blood flow	1999	8.1788	2008	2011	
mri	1999	8.7261	2008	2014	
recognition	1999	4.6172	2008	2016	
adolescent	1999	3.6096	2008	2009	
phenomenology	1999	9.0207	2008	2014	
macular degeneration	1999	3.1968	2009	2014	
neuropathology	1999	3.4948	2009	2012	
follow up	1999	5.8447	2009	2013	
complex visual hallucination	1999	4.677	2009	2016	
quetiapine	1999	3.6532	2010	2016	
pathology	1999	5.2104	2010	2013	
l dopa	1999	3.2897	2010	2012	
epidemiology	1999	5.1796	2010	2011	
dlb	1999	5.1701	2010	2013	
contrast sensitivity	1999	3.8881	2011	2014	
discrimination	1999	4.5838	2011	2012	
event related potential	1999	3.5812	2011	2012	
eeg	1999	5.9712	2011	2014	
efficacy	1999	4.7751	2011	2013	
population	1999	6.0123	2012	2016	
deficit	1999	3.7813	2012	2013	
working memory	1999	4.531	2012	2014	
rem sleep	1999	3.5098	2012	2014	
drug induced psychosis	1999	4.1121	2013	2016	
rating scale	1999	6.3947	2013	2018	
memory	1999	7.2837	2013	2015	
impairment	1999	3.2156	2013	2015	
neuropsychiatric symptom	1999	11.91	2014	2020	
diagnostic criteria	1999	9.4286	2014	2020	
fmri	1999	9.1494	2015	2020	
auditory verbal hallucination	1999	10.0313	2015	2020	
mechanism	1999	3.4443	2015	2016	
people	1999	4.6497	2015	2018	
activation	1999	4.2145	2015	2017	
scale	1999	3.7291	2015	2020	
illusion	1999	3.8143	2015	2020	
patient	1999	5.1895	2015	2016	
parkinson disease	1999	4.0119	2016	2017	
visual cortex	1999	5.3741	2016	2018	
disease	1999	4.4676	2016	2017	
risk factor	1999	4.3317	2016	2017	
nonmotor symptom	1999	6.4546	2016	2017	
mild cognitive impairment	1999	7.7521	2016	2018	
impulse control disorder	1999	6.5227	2017	2020	
sleep behavior disorder	1999	5.8812	2017	2020	
default mode network	1999	5.0732	2017	2020	
metaanalysis	1999	8.104	2017	2020	
functional connectivity	1999	11.6008	2017	2020	
model	1999	5.7835	2018	2020	
association	1999	3.8779	2018	2020	
experience	1999	5.9387	2018	2020	
management	1999	6.5895	2018	2020	
risk	1999	5.4201	2018	2020	

Figure 5 The top 104 burst keywords. The blue line represents the timeline from 1999 to 2020, while the red line stands for the years when a keyword has burst.

remarkable finding that links the clinical and pathological features of DLB together [70].

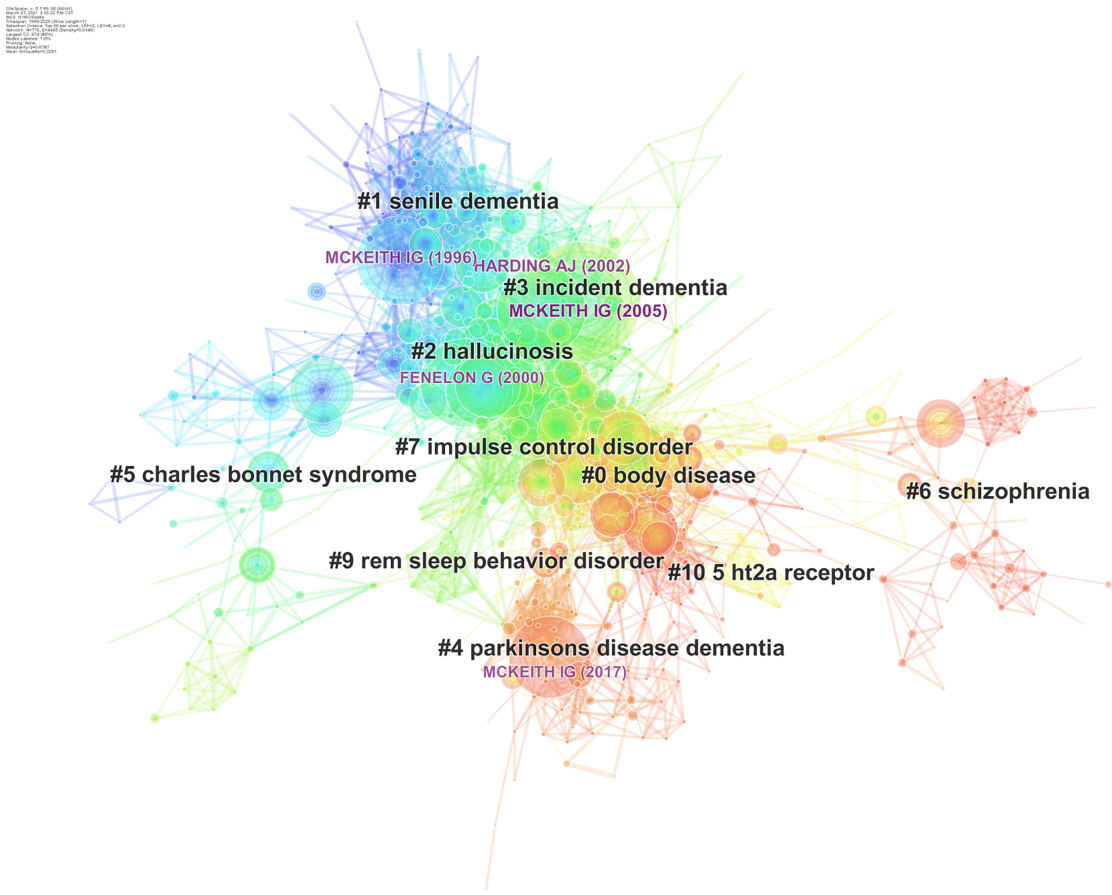


Figure 6 A network of 776 co-cited references representing citation patterns of top 50 articles per year between 1999 and 2020. The overall structure can be divided into three major parts: the upper left part of the network is essentially in blue, which represent the co-citation between 1999 and 2005. The central part of the network is mainly in green and yellow, which indicates the relationship is probably constructed in the middle 7 yr from 2006 to 2012. The bottom right part is predominantly in red and connections were formed credibly in the most recent 8 yr, that is 2013-2020.

Pivot articles

Pivot articles often refer to gateway articles between two densely connected subfields with a unique position. This type of articles can provide insights into emerging trends. The top ranked article by centrality is Aarsland D (2002) in Cluster #1, which has a centrality of 0.09. This double-blind, randomized, placebo-controlled study included 14 PDD patients to study the safety and effectiveness of the cholinesterase inhibitor donepezil in the treatment of PDD. This study lasted for 20 wk and finally they found that donepezil is safe and effective, also it does not worsen motor symptoms of PD [71]. This outstanding discovery has important therapeutic implications for PDD. The second one is Goetz CG (2011) in Cluster #0, with centrality of 0.08. Goetz *et al*[72] followed up 60 patients with PD but without hallucinations at baseline for more than 10 years. VH was found to dominate in early hallucination profile. This discovery revealed the outstanding position of VH in PDP. The third is Cummings J (2014) in Cluster #0, with centrality of 0.07. Cummings *et al*[46] conducted a randomized controlled double-blind trial on patients with PDP and concluded that this population can achieve benefit from Pimavanserin, a selective serotonin 5-HT2A inverse agonist, which is the only U.S. Food and Drug Administration-approved medication for PDP [23]. This study was a phase 3 trial that marks a critical breakthrough in the treatment of PDP, in which VH is a common symptom[73].

Burst articles

The importance of burst cannot be overemphasized. Through burst testing of all cited articles, we easily found that Mckeith IG (2017), Mckeith IG (1996), and Mckeith IG (2005) are on the top of the diagram. They are the milestones in relation to DLB. We discussed the last two articles in front part. The top one was Mckeith IG (2017) in Cluster #4. Mckeith *et al*[74] renewed the consensus report of DLB in 2017. Compared with the 2005 edition, the 2017 edition clearly distinguished clinical features and biological markers. According to different clinical features and biological markers, the

Ref.	Strength	Begin	End	1999-2020
Waters *et al*[59], 2014	19.3898	2015	2020	
Pagonabarraga *et al*[29], 2016	19.2073	2016	2020	
Onofrj *et al*[80], 2013	12.6453	2014	2020	
Mckeith *et al*[74], 2017	44.1227	2018	2020	
Lenka *et al*[81], 2015	13.3785	2016	2020	
Vann Jones al[82], 2014	12.621	2017	2020	
Goldman *et al*[83], 2014	14.5101	2015	2020	
Ffytche *et al*[73], 2017	18.9805	2018	2020	
Cummings *et al*[46], 2014	21.7452	2016	2020	
Archibald *et al*[84], 2011	12.3342	2014	2020	

Figure 7 The top 10 references that retained citation burst until 2020.

diagnosis was divided into probable and possible DLB. Consistency of the diagnostic criteria for DLB will be more conducive to further research on DLB.

It is valuable to examine the citation burst in more recent articles while eliminating the overshadow burst of those landmark articles. The top 10 references that retained citation burst until 2020 are shown in Figure 7, which anticipates emerging trends in the future. In general, a new emerging trend involves PD with VH. Waters F (2014) is a relatively early article comparing VH in different diseases[59]. This article opened up a new dimension in VH research. Although many hypotheses have been proposed to explain the mechanism of VH, and many imaging and electrophysiological studies have partly proved these hypotheses; it is still unclear whether VH in different diseases has the same mechanism, and further research is needed. Pagonabarraga J (2016) is the only article that had citation burst as soon as its publication. PD minor hallucination is not a newly found phenomenon in PD but is underestimated because previous research on PDP focused on the study of well-structured VH. Pagonabarraga *et al*[29] reported that minor hallucination is the most frequent symptom in PDP and may even occur before the onset of parkinsonism. The third paper was Onofrj M (2013). This paper reviews the hypothetical mechanisms of VH in PD and DLB. To date, three predominant mechanistic models have been presented: a disturbance between top-down and bottom-up aspects of visual perception[1,75]; chronic deafferentation causing hyperexcitability to cortical structures involved in vision[3,76]; and the misattribution of internal imagery[59,77,78]. The authors tend to identify with the attention deficit network model as mentioned before.

Structurally and temporally significant articles

Sigma is defined as: $(centrality + 1)^{burstness}$, which can simultaneously measure a cited reference's structural centrality and citation burstness. Teunisse RJ (1996) is at the top of the list, which objectively describes the characteristics of CBS by using a semi-structured interview[79]. The advanced nature of this article lies not only in the formation of the prototype semi-structured interview of VH but also in the occurrence of CBS, which is partly due to sensory deprivation and low arousal. The second was Cummings J (2014) in Cluster #4, Mckeith IG (2005) ranked third in this part and their importance is self-evident.

CONCLUSION

Through systematic analysis of the literature of VH over the past 22 years, we found that with the yearly progress of research on VH, its mystery has been gradually unveiled. Current research mainly focuses on neuropsychiatry. Countless countries,

institutions, and authors have collaborated together and contributed to this field. North America, Europe, Asia and Australia showed outstanding contributions, and Dr. Taylor JP and Dr. Aarsland D are the most active contributors. Several research hotspots in the field of VH were detected in the recent research. The neuropsychiatry symptom and MRI function connectivity have been paid much attention. In the field of VH, neurodegenerative diseases, especially PD and DLB, were found to be widely studied. We believe that research on these two diseases will continue to advance the field of VH.

Although VH is of clinical importance, and its pathophysiology or treatment is mainly focused on single diseases and its mechanisms remain unclear. Additional clinical studies are required to provide higher evidence-based support for the diagnosis and treatment of VH. We investigated the basic literature related to VH and concluded that the small number of such studies is partly caused by difficulty in inducing and testing VH in animal models. Further efforts are required in this direction to obtain profound insights into the mechanisms that underlie VH. This issue will have important pathophysiologic and possible therapeutic implications in the future.

ARTICLE HIGHLIGHTS

Research background

Visual hallucination (VH) refers to a spontaneous visual perception without corresponding external stimuli and often occurs in ophthalmological and neuropsychiatric disorders. It is associated with poor life quality, increased patient hospitalization, and nursing home admission.

Research motivation

To date, there is a lack of scientometric analysis of the research on VH.

Research objectives

To objectively summarize the features of VH research and gain insights into the emerging trends for research on VH.

Research methods

CiteSpace V was used in this article. Publication outputs, document types, geographic distributions, co-authorship status, research hotspots, and co-citation status were analyzed. A total of 2176 original articles and 465 reviews were included in the database downloaded from the Web of Science Core Collection.

Research results

The results showed that most publications can be classified into neurology, sports and ophthalmology studies. In addition, North America, Europe, Asia, and Australia published the most documents. Some well-known authors have always had a leading role in this field; meanwhile, new authors keep emerging. A relatively stable cooperation has been formed among many authors. Furthermore, neuropsychiatric symptom and functional connectivity are the top hotspots. Research on VH in dementia with Lewy bodies and Parkinson's disease (PD) have received much attention.

Research conclusions

Studies on VH in PD are likely to be the new emerging trends in the future, especially the mechanism of VH.

Research perspectives

More large-scale clinical and in-depth basic research studies are required to better understand the mechanisms underlie VH, which will contribute to our understanding of pathophysiology and therapy in VH.

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Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 September 19; 11(9): 507-680



Published by Baishideng Publishing Group Inc

WJP World Journal of Psychiatry

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Peer Reviewer of *World Journal of Psychiatry*, Xin-Ke Li, PhD, Associate Professor, College of Medical Informatics, Chongqing Medical University, Chongqing 400016, China. zmdcg@126.com

AIMS AND SCOPE

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The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xu Guo*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
September 19, 2021

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World Journal of Psychiatry

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World J Psychiatr 2021 September 19; 11(9): 507-516

DOI: 10.5498/wjp.v11.i9.507

ISSN 2220-3206 (online)

EDITORIAL

Future of processing and facilitating change and learning

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Author contributions: Steinmair D and Löffler-Stastka H contributed to concept, writing, discussion, critical revision, editing, and review of the literature.

Conflict-of-interest statement: Steinmair D and Löffler-Stastka H have nothing to disclose.

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Manuscript source: Invited manuscript

Specialty type: Psychology

Country/Territory of origin: Austria

Peer-review report's scientific quality classification

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Abstract

The field of the sciences of the mind is evolving fast. With the diversification of knowledge and accumulation of data, often lacking integration and reproducibility, questions arise. The role of critical thinking and research is evident. As the science of the unconscious, psychoanalysis provides a method and theory to understand human minds and mentalities, helping the patient know his mind and transform action into reflection. Mental activities, including social skills, develop in the social context, depending on the social environment's demands and resources put onto the individual. Encoding emotional signals, markers of meaning for the individual, is ontogenetically necessary and has influences on memory encoding. Beyond theoretical understanding, implicit relational knowledge is actualized in the therapeutic setting. With a strong focus on experiencing emotional reconsolidation of memories, previous relationships' repercussions are enriched with broadening viewpoints in the analytic environment. The long-term effects of psychotherapeutic treatments have been examined. A sufficient explanation of the specific factors contributing to success or an answer when an impact is lacking is still under investigation. When investigating subliminal and implicit mechanisms leading to memory reconsolidation and the formation of functional object relations and interaction patterns, the focus is set on affective interplay and processing prior/during and after social interactions. The present paper discusses which parameters might contribute to the reshaping of memories and the linkage of memory with the emotional load of experience. Providing insights into such dynamic mental phenomena could enhance process research by investigating moment by moment interactions in psychoanalysis, treatment, and learning processes. Due to the research subject's complexity, different research methods and integration of associated research fields are required.

Key Words: Psychoanalysis; Hermeneutic circle; Evidence-based medicine; Bias; Affective interplay; Micro-process

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Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: April 20, 2021
Revised: April 24, 2021
Accepted: August 2, 2021
Article in press: August 2, 2021
Published online: September 19, 2021

P-Reviewer: Hosseini MS
S-Editor: Liu M
L-Editor: Filipodia
P-Editor: Ma YJ



Core Tip: The mind's ability to interact and assess the external world's reality and integrate new experiences into existing conceptions is determined by the affective load the respective interplay is assigned. Gaining a picture of the world at an acceptable reliability level requires a curious mind and openness for a discursive dispute with encountered findings.

Citation: Löffler-Stastka H, Steinmair D. Future of processing and facilitating change and learning. *World J Psychiatr* 2021; 11(9): 507-516
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/507.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.507

INTRODUCTION

"The only true wisdom is in knowing you know nothing." – Socrates.

The illusion of certainty is constantly eroded when the amplification of questions is generated by research. Nevertheless, integrating scientific findings following an interdisciplinary approach is as challenging as inspiring, even more when dealing with a presumably still unknowable research object like the human mind. Creating a scientific dialogue dedicated to integrating balanced evidence while still constantly questioning results for their probability towards an approximation to truths requires openness to innovation. This dialogue leads to an integration of different perspectives; all concerned with overlapping research topics.

THE CIRCLE OF UNDERSTANDING

Being in the world involves acquiring experience, knowledge, and assumptions. Only from the observer's background, it is possible to enter a circle of understanding and re-experience in practice the hermeneutic circle. Developing a sense of the whole means acquiring a better sense of each part – the interpretation of findings depends on the conceptions and vice versa.

Psychodynamic theorizing and therapeutic work explore the unconscious elements not intelligible to conscious thinking but impacting our cognitive and affective abilities. Therapeutic work makes part of applied sciences to apply care based on up-to-date scientific findings continually. It contributes to research by generating a hypothesis and collecting data again, feeding back to research and quality control. "How do we know what we know" remains a sophisticated question, especially when it comes to 'implicit' and 'embodied' knowledge like social skills, relational knowledge, and interactional patterns.

Relevance to the daily routine and therapeutic work is evident as investigating mechanisms of change in this field determines patients' future options and the therapists' attitudes toward what she/he can influence. Generating meaning and giving value to one's life is something very individual and so are conceptions regarding the outcome. However, attachment to relevant others and life itself is often disturbed in mental disorders. Mental conditions confound and trouble emotional well-being and overall psychosocial functioning, with innumerable consequences on a person's path of life, catapulting them in an awkward position. Compassion fatigue marks the borders of empathy and resilience even of socially skilled and socially minded persons.

LEVELS OF EVIDENCE

To answer clinical questions and support clinical decision-making recommendations, evidence-based medicine should rely on the highest level of evidence available. Expert opinion and case reports are at the lowest level of evidence followed by case series. However, when it comes to the relevance of an individual case, this is not only determined by the incidence of the condition in question and thus by the possibility of carrying out extensive investigations (*e.g.*, in rare diseases). To follow a hypothesis-

generating approach, such study designs including qualitative methods (video- or text-analyses, interviews, *etc*.) can be of specific value and can be combined in a mixed-methods design to build a clinical theory - of course without claiming the stance of a scientific theory. Strong recommendations demand several adequately conducted randomized controlled trials and systematic reviews/meta-analyses on the research question. However, consistent evidence from lower-level studies (high-quality prospective cohort study with adequate power) and evidence from a lesser quality type of evidence with a predefined study design (*e.g.*, retrospective cohort study, a case-control study) support a strong recommendation[1]. The quality of possible findings in a meta-analysis depends on the quality of available evidence. Nevertheless, both approaches, a quantitative, natural scientific and a more qualitative, social scientific or even including the humanities, can be interesting for the research field of processing and facilitating change and learning, but we have to take the different levels of evidence into account.

Interpretation of knowledge from different levels of evidence can be challenging. However, when prioritizing information, the need for randomized controlled trials to improve evidence is relevant for psychodynamic theorizing. Confirmation[2] and publication bias[3] can only be avoided by reproduction of results in large systematic replication projects, transparency and completeness in reporting methods, data, and analysis in a scientific publication[4,5]. To avoid constructed consensus, Socrates developed the Socratic dialogue as a form of cooperative argumentative dialogue based on asking and answering questions to stimulate critical thinking[6]. Awareness of the complexity of investigations, of the questionability of truth and value of one's own opinions, leads to careful and in-depth thinking[6]. Popper's concept of critical rationalism as a method of inquiry claims that scientific theories should be criticized; a hypothesis must be subjected to tests that might falsify them[7,8]. Critical rationalists believe in progress without believing in the concept of truth in an absolute sense. However, in postmodernism, a diversity of voices is accepted as an acceptable endpoint of scientific research[8]. The human mind's ability to falsify hypotheses might be limited by its premises as its ability to generate them. Anti-positivists doubted the existence of facts. A problem-oriented, or even case-based, approach, instead of focusing on a method-oriented approach, has been claimed by both postmodernists and critical rationalists[8].

THE SCIENCE OF THE UNCONSCIOUS

In his search of the genesis of human knowledge and the role memory has in our having experience, Freud[9] concluded that plenty of human mental processes might happen unconsciously but influence behavior. In his everyday work, Freud[9] observed clinical phenomena and effects worth investigating further, thus facilitating subsequent research, with his theories also being subject to controversy. In his analysis of symptoms, he postulated that each of them makes sense when the mind's operations taking place below the conscious awareness level are considered (also compare[10]). Drives connected with basic needs (*i.e.* basic biological instincts) and societal demands posed to the individual by environments and context form human personalities, intrapsychic structures (ego, id, and super-ego), and mental abilities. Social and human science methodologists developed a multitude of research strategies, termed 'qualitative'. With Lacan[11], among other psychoanalytic theoretical developments, psychoanalytical science became a symbolization process and a way of obliterating and dissolving the phenomena of life. The imaginary realm (*e.g.*, images, shapes) is transformed in the symbolical realm of scientific experience (*e.g.*, measurement, numbers, formulae, methodological standards)[12] (Figure 1).

Contemporary views on whether research has a role in justifying and developing psychoanalytic theory and the limitations of research in this field root in a controversy with a long history[13]. Psychiatry, conceptualized as applied clinical neuroscience, had been focusing on pharmacotherapy in the 1990s. In contrast, integrating the psychoanalytic method into other psychological methods and establishing a research culture had been missed[14].

Nevertheless, clinical observations were invaluable to all known thinkers in this field. Repeated interactions with the caregiver and relevant others in early childhood shape how reality is experienced and perceived. Those affectively loaded and lived experiences result in implicit knowledge and assumptions and determine later behavior (*i.e.* patterns)[15]. That is why infant research has a long history within psychoanalysis[16-20].

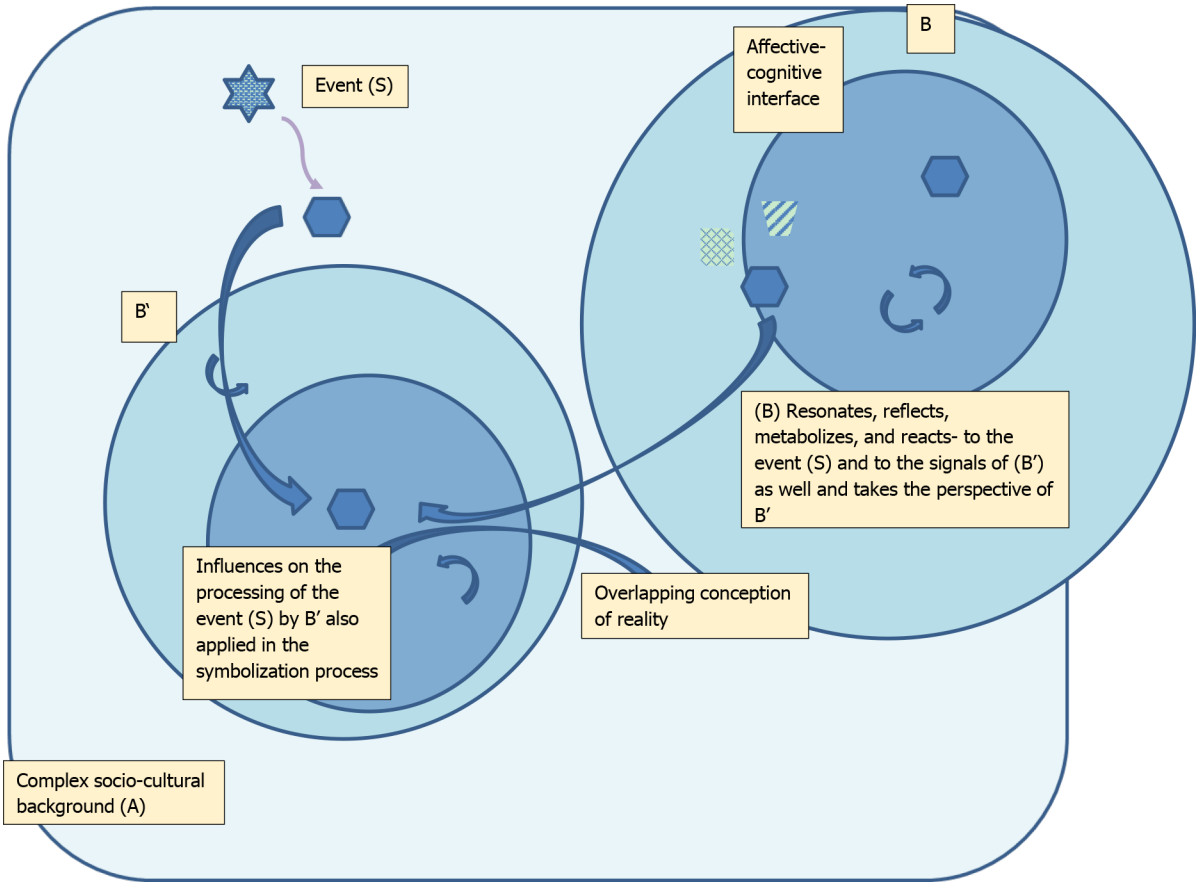


Figure 1 Symbolization process. Within a more complex sociocultural background (A), two individuals meet (B, B'). Something (S) affects them both in their (shared conception of) reality. An individual's behavior and inner states and reaction to this stimulus depend on its own symbolization abilities and experiencing. This processing evolves in tight interrelation with others and happens on a somatic and a cognitive layer. The relevant other (B) resonates, reflects, metabolizes, and reacts to the event (S) and to the signals of (B') as well and takes the perspective of B'. This reaction again influences the processing of the event (S) by B', also applied in the symbolization process.

PSYCHOTHERAPY RESEARCH

Adaptation to reality is one of the principal goals in psychoanalytic therapy, with reality as the derivation point of unconscious fantasies[9] exposed by the therapeutic work. Psychodynamic work considers subliminal signals (*i.e.* enacted through language, gesture, facial expressions) and latent perceptions of those stimuli. Importance of unconscious and embodied knowledge in the processing of such perceptions applies. Psychodynamic interventions aim at reshaping cognitive processing (*e.g.*, perception, attention, and memory)[21] by creating new viewpoints and experiences in the (analytic) environment.

Several high-quality studies reviewed in an updated meta-analysis have shown the efficacy of short-term psychodynamic therapy for depression and its equivalence with other psychotherapies[22-24]. However, several reviews with very high effect sizes had to be excluded from this analysis due to their statistical methodology. Long-term psychoanalytic therapy effectiveness is supported by evidence from systematic reviews of empirical studies[25]. Regardless of these findings, concerns about the consistency of the research methodology have been raised. Due to the lack of meta-analyses reviewing robust, high-quality data, high-level evidence is missing[25]. Overall, identifying predictors for long-term effects would help yield hope for individual patients and allocate treatments. Nowadays, health care providers demand the highest achievable evidence when deciding upon the allocation of resources. When confronting the efficacy of cognitive-behavioral therapy and psychodynamic therapy in treating major depression, the two methods applied in the randomized controlled trials showed no significant differences but were equally effective[23]. However, when long-lasting effects (3 years) were investigated, psychoanalytic therapy was better, possibly due to a dose effect[26]. Additionally, mediators predicting treatment success specific for each treatment method have been proposed[27-31]. Investigating dreams and patients' fantasies and focusing on memories or reconstructions of childhood were

found to explain some of the differences between the two methods.

When creating common ground in psychotherapy research, this involves many therapeutic approaches, claiming to have the recipe for healing the human psyche. One of the characteristic traits of humans, most probably distinguishing them from other primates, is their ability to form societies and carry on negotiations between different groups within individual societies and at an international level. The ability to hypothesize and adopt different perspectives to understand other viewpoints (*i.e.* mentalizing) is necessary.

As to psychotherapy research, given that many different approaches lead to improved symptoms, common factor models (including alliance, empathy[32], attitude [33], expectations, cultural adaptation, and therapist differences)[34-36] have been proposed, including the clients' contributions[37]. Essential skills for all psychotherapists are relationship skills, attachment, and emotional intelligence abilities. For psychodynamic therapy, technical neutrality was found to correlate with success[38].

INTEGRATION OF KNOWLEDGE

Nowadays, embedding psychodynamic thinking with an evidence-based approach aims at integrating different kinds of research, looking at cognitive processes from different perspectives.

The constant questioning of "truths" leads to openness to innovations and engagement with associated research fields (*e.g.*, neuropsychology, neurosciences, communication-sciences). As outlined above, a mixed-method approach is necessary when generating evidence in a real-world scenario. The choice of the method depends on the research question, but independent of the method considered, quality depends on preventing bias (*e.g.*, recall bias, selection bias, observation bias, confirmation bias, and publishing bias). As mentioned above, the approach should be a problem-solving one. Collaboration, support (*e.g.*, methodological support, guidelines), peer review, and open science reforms call for openness in the scientific discourse[39].

Developing substantial research questions requires excellent knowledge of the investigated research topic and the problem identified. The uncertainty and complexity of knowledge and parties involved limit the academic debate, and already the possible questions impact answers. Thus, integrating new theories and strains of expertise and strategies in existing frameworks and dynamic systems (*e.g.*, *via* a public/patient involving design) requires an adequate understanding of the system, influencing factors, and a generalization across its states and the ones of the observing unit/system. This integration of findings might be challenging and time-consuming [40]. Scientific theorizing involves acknowledging uncertainty and expressing the limitation of results.

Applying this to the example of research in emotion and behavior will demonstrate the rise of a new research field by integrating different approaches and awareness of limitations in research. Emotion has been a mainstream topic in the last decades[41]. Psychoanalysts and neuropsychologists have equally been interested in understanding emotional processes. The interest in this research field is understandable because of the influence emotion has on cognitive abilities. This impact is especially true in directing an individual's attention, perception of reality, motivation, and memory[42]. Human emotions determine how an individual uses its resources, and they have importance not only when triggered by internal stimuli but also when interacting with external triggers (compare, *e.g.*, mentalization based therapy)[43].

Generation of meaning is bound to the interplay between individual and (social) environment under specific conditions and frames memory traces. Each selection between different action options (and thoughts) influences subsequent decisions. When relying on experience, actualization is facilitated if adaptation to the current environment is perceived as sufficient. Implicit bias refers to unconscious assumptions, categories, and attitudes influencing our perception and appraisal[42]. Cognitive bias enables fast cognitive processing and roots in evolutionary advantage arising from this stereotype judgment, with evident affective influences.

The world of science seeks to study phenomena through observation and experiment. The impact of the flexibility of analytical approaches was investigated recently for the field of neuroimaging: the analysis of a single neuroimaging dataset by many teams showed substantial variability despite significant consensus in activated regions [42]. The authors stress the importance of validating complex workflows and analyzing data[42] through different research teams, taking into account implicit bias. Also, for the field of explainable artificial intelligence, a paradigm shift has been

suggested to avoid confirmation bias and increase transparency and validity[44].

Emotion theories from various research fields were concerned with components of emotional processes. Emotions include preceding mental and bodily states, appraisal and consequences like consciousness, generation of symbolic meaning, and/or enactment *via* behavior. The importance of process in addition to outcome research has been emphasized. Looking at micro processes prior/during and after social interactions makes sense in emotion research as emotional reactions arise during interactions with others and are perceived and regulated moment by moment[45-47].

As the science of the unconscious, psychoanalysis investigates human minds and mentality, aiming to provide an environment for the transformation of enactment into reflection, preventing recurring patterns if identified as destructive or harmful[48]. This process of adaptation occurs in the individual as well as in society. However, how does this happen? An "analytic environment" provides an actualization of memories and related implicit and unconscious knowledge and affective linkages. The psychoanalytic method aims at broadening the field of experience and perception. Providing a revalidation and reinterpretation of existing viewpoints leads to freedom of thought and action and reshaping memories or appraisal. Integration of so far indigestible contents in a more favorable narrative leads to a changed perception of reality and perspectives. The focus is on the affective interplay and processing in the actualized situation, thus demanding time to analyze ongoing interactions[47,49]. Leading affects in the early dyadic interplays directly affect conceptions of the self. A child's internal abilities to cope with reality depend on whether specific representational structures (self, others, relationships) have been created in the early interactions[50,51]. Interactional patterns are socially transmittable, and their modification is challenging.

Psychotherapy research is concerned with process and outcome investigation of how specific factors contribute to therapy success or alliance rupture and failure. Observational research often assumes that behavior is more or less proving of mental and affective states. However, modifiers and moderators must be considered when aiming at attributing results to specific therapeutic interventions. For mice, facial expressions have been linked to emotional states and their neuronal correlates[50,52]. While in the mouse model and under laboratory circumstances, this might be more straightforward, generalization to real-life scenarios requires caution when interpreting findings.

When it comes to investigating persons with disturbances or diseases of their mental health, their vulnerability[53] must be acknowledged in therapy as well as when conceptualizing research[54,55] (1949 Nuremberg Code, updated in the 2008 World Medical Association Declaration of Helsinki, and in the 1979 Belmont Report). On the other hand, excluding persons only because they belong to vulnerable groups has been discussed as equally unethical and contributing to research bias[56,57]. Each case must be considered, especially when dealing with persons with (temporarily, fluctuating, or permanently) impaired mental state. In psychoanalytic therapy, investigation of therapy dropouts revealed that multiple factors contribute to the decision to continue or to dismiss treatments. Goals, readiness to change, awareness and insight capacity, resistance, and transference are well-known factors[55]. However, when Lacan[57] attempts to conceptualize psychoanalytical ethics, he places the problem of desire at the center of his ethics[56]. "At every moment we need to know what our effective relationship is to the desire to do good, to the desire to cure." Lacan[57] keeps reminding us that the sphere of human subjectivity, including unconscious fantasies, is a dimension the analyst cannot pretend to know. Lacan[57] emphasizes that not only the patients' unconscious wishes are present, but also the analyst's own desires. Acknowledging this is the starting point in preventing the psychoanalyst's application of personal reality and desire as a normative ideology to the patient[58]. This includes "hidden agendas of economic power and status" and morality[56].

Self-related processing, the wish to be the agent of one's actions in the world, and orientation towards relevant others (*i.e.* innate attachment motive) through repetitive interactional interplay leads to creating social bonds as to the human's impact on the environment. Interactive resonance contributes to attachment formation with relevant others[46]. Medical knowledge integration is ambitious due to the heterogonous field involving biological, behavioral, and social sciences providing data (bottom-up)[59]. Top-down organismic systems medicine has been proposed as an integrative approach [40].

When merging psychoanalytical with neuroscientific conceptions, both assume that major adaptations and developments related to cognitive abilities merely take place in the first decades of life. This goes in hand with current attempts to detect and treat vulnerable subjects already early in their life to prevent mental disorders later on[37]. Following systems theory, a rather integrative approach, and complex systems can

only be understood in their context, influencing each other[60] through a web of connections depending on their complexity.

Subliminal affective reactions can be hints for targeting specific interventions[61-63]. The ability to infer mental and affective states evolves early in life, but different interpersonal and arousal contexts influence available strategies[64]. When dealing with a subject's memories, this is supposed to be emotionally challenging because only subjectively valuable content is stored. However, when experiences are overwhelming, accessibility of memory content might be reduced. Containment also depends on the attitudes and competencies of the containing person[33,48]. Memories are not unchangeable. However, defense against arbitrary manipulation is adaptive and intelligible due to obvious reasons. Psychodynamic therapies aim to explore and interpret internal conflicts to assist people when earlier experiences influence a destructive and distorting way on present options[63].

Providing an opportunity to model oneself by reconsidering our mind, various core factors apply. This remodeling would imply a reconceptualization of the self and others and the relationships between them and anchoring this process in the embodied self[64]. When interacting with the world, self-representations and world-representations are actualized. Hence, psychotherapy constitutes a setting where this process is supposed to happen in a sphere of expanded subjectivity (involving the therapist), considering rational aspects and experiencing[19,40,46].

CONCLUSION

In conclusion, integrating relevant findings into psychoanalytic theories requires a top-down approach (*i.e.* a meta-theory) constantly metabolizing up-to-date empirical evidence. Thus, differentiation of knowledge about mental conditions evolves dynamically in a sphere of unification of multiple features contributing to the whole, also very subjective contributions to the topic of facilitating change.

Almost any phenomenon can be studied qualitatively and quantitatively. However, applied techniques determine results, and choosing the adequate research method according to the scope and research question is critical for gaining an in-depth picture of the addressed topic.

ACKNOWLEDGEMENTS

We thank the reviewers for comments that significantly improved the final version of the manuscript.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 September 19; 11(9): 517-529

DOI: 10.5498/wjp.v11.i9.517

ISSN 2220-3206 (online)

REVIEW

Binge eating and psychostimulant addiction

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Author contributions: All named authors made an active contribution to the conception, design and drafting of the review article; Blanco-Gandia MC and Montagud-Romero S performed the majority of the writing and created the figures; Rodríguez-Arias M designed the outline and coordinated the writing of the paper; Blanco-Gandia MC, Montagud-Romero S and Rodrí guez-Arias M critically reviewed the content and approved the final version for publication.

Supported by Generalitat Valenciana, Conselleria Educacion, Direccion General de Universidades, Grupos de Investigación de Excelencia, No. PROMETEO 2018/132; Ministerio de Sanidad, Servicios Sociales e Igualdad, Delegación del Gobierno para el Plan Nacional Sobre Drogas, Proyectos de Investigación sobre Drogodependencias, No. 2018I013; and Instituto de Salud Carlos III, Red de Trastornos Adictivos y Unión Europea, Fondos FEDER una manera de, No. RD16/0017/0007.

Conflict-of-interest statement: The authors declare that they have no

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Abstract

Many of the various factors, characteristics, and variables involved in the addictive process can determine an individual's vulnerability to develop drug addiction. Hedonic eating, based on pleasure rather than energy needs, modulates the same reward circuits, as do drugs of abuse. According to the last report of the World Health Organization, the worldwide obesity rate has more than doubled since 1980, reaching especially critical levels in children and young people, who are overexposed to high-fat, high-sugar, energy-dense foods. Over the past few decades, there has been an increase in the number of studies focused on how eating disorders can lead to the development of drug addiction and on the comorbidity that exists between the two disorders. Herein, we review the most recent research on the subject, focusing especially on animal models of binge eating disorders and drug addiction. The complex profile of patients with substance use and binge eating disorders requires an integrated response to dually diagnosed patients. Nutritional patterns should be considered an important variable in the treatment of substance use disorders, and future studies need to focus on specific treatments and interventions in individuals who show a special vulnerability to shift from one addiction to the other.

Key Words: Binge eating; Psychostimulant; Dopamine; Obesity; Reward; Addiction

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Core Tip: In recent years there has been an increased interest in the relationship between food rewarding properties and drug abuse. Binge eating and drug abuse are associated with loss of control and share clinical morbidity. The comorbidity complicates the evaluation and treatment of both disorders, affecting inhibitory control

conflicting interests.

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Manuscript source: Invited manuscript

Specialty type: Substance abuse

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 13, 2021
Peer-review started: January 13, 2021
First decision: May 5, 2021
Revised: May 13, 2021
Accepted: July 27, 2021
Article in press: July 27, 2021
Published online: September 19, 2021

P-Reviewer: Raghow R
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Guo X

and decision making. This is the first mini-review exploring the most recent research about how bingeing on palatable food can potentially influence vulnerability to develop psychostimulant addiction. It includes the behavioral and neurobiological commonalities between binge eating disorder and drug addiction, especially focusing on recent animal studies.

Citation: Blanco-Gandia MC, Montagud-Romero S, Rodríguez-Arias M. Binge eating and psychostimulant addiction. *World J Psychiatr* 2021; 11(9): 517-529
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/517.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.517

INTRODUCTION

The aim of the present review is to throw light on the similarities between binge eating disorder and substance use disorders by exploring the most recent research about how bingeing on palatable food can influence vulnerability to the development of psychostimulant addiction. We address how the two disorders co-occur, and discuss the need for new forms of treatment and therapies that approach the problem as a dual pathology.

In all species of the animal kingdom, nutrition is crucial for the maintenance of adequate energy stores for survival. Mammals need to maintain a stable body temperature, and as they have a high metabolic rate, they require a constant supply of large amounts of energy[1]. That is the reason why mammalian brains have evolved to develop several neuronal systems that drive feeding behavior, with the rewarding nature of eating being one of the most potent drives behind feeding[2]. Beyond the homeostatic regulation of food intake, and in order to promote survival, the complex neural networks within the brain drive individuals to seek the most caloric foods. During evolution, our organism has developed in a context of nutritional shortage, so we have an innate biological preference for that type of food. That is why palatable foods high in fat, sugar, and salt induce a potent release of dopamine in our brain reward system, producing a great feeling of pleasure[3].

As a consequence of the brain's bias towards palatable food, overeating and obesity are global diseases of our modern society, even though both are preventable. For many years, malnutrition was a common problem, but now, according to the most recent report of the World Health Organization[4], worldwide obesity rates have more than tripled since 1975, and it now kills more people than undernourishment. In 2016, 39% of the world population over 18 years of age was overweight and 13% were obese. This problem is especially critical in children and young people, who are more vulnerable to inadequate dietary habits and are overexposed to high-fat, high-sugar, high-salt, energy-dense foods of lower nutritional quality. In 2016, 41 million children under 5 years of age worldwide were overweight or obese. The progressive and continuous increase in metabolic diseases and overweight is related to obesogenic environmental factors, such as the high number of fast food establishments, the decrease in physical activity associated with the sedentary nature of many forms of work, transportation choices, and increased urbanization[4,5]. The rise in obesity rates worldwide has encouraged extensive research to improve our understanding of the problem, particularly the excessive intake of food, and especially that of sugary and fatty foods, which has become a serious health problem for our society.

The 21st century society is characterized by the consumption of ultraprocessed food that is high in fat and sugar and is often eaten for pleasure rather than survival; in this context, Gold[6] defined "hedonic eating" as *eating based on pleasure rather than energy needs*. Research to date shows that hedonic eating modulates neural mechanisms related to reward processing[7], the same circuits activated by drugs of abuse, which explains the maintenance and escalation of this behavior. The brain reward system is designed to play a crucial role in basic survival activities, such as eating, sex or sleep [1]. However, we are currently facing a situation in which palatable food not only supports our survival but also modulates our brain function and behavior.

Drugs of abuse target the abovementioned reward system, inducing an overstimulation of the circuitry that eventually overrides the pleasurable effects of other basic activities[8]. As with other psychiatric disorders, not all humans have the same risk of

developing an addiction, and the risk varies considerably from one person to another. There are many different factors, characteristics, and variables involved in the addictive process, and they determine an individual's vulnerability to develop this disease. In general, the more risk factors found in a person, the greater is the probability of developing a substance use disorder after taking drugs occasionally[9]. Among the environmental and lifestyle variables under investigation in recent years are nutritional habits and eating patterns, which not only contribute to the obesity epidemic, but also affect our mental health and can lead to the development of a substance use disorder[10].

The latest research suggests that both drug addiction and obesity are disorders in which the value of drug or food reinforcement, respectively is abnormally increased in relation to and at the expense of other reinforcements[7,10]. Both drugs and food have powerful rewarding effects mediated by increases in dopamine release in the limbic system that, under certain circumstances or in vulnerable subjects, can alter the homeostatic control mechanisms of hunger and satiety[7,11,12]. For example, it has been shown that individuals with a substance use disorder or obesity have a reduced number of dopamine receptors in the nucleus accumbens[7], and the neuroadaptation has been directly related to a decrease in the basal activity of the frontal regions involved in reward and inhibitory control[13].

Adolescent populations today are often characterized by abnormal dietary habits and lower levels of physical activity, resulting in an increased percentage of overweight adolescents that will later become obese adults. Apart from the risk of developing obesity-derived cardiovascular diseases such as diabetes, it is important to bear in mind that adolescents are more prone than adults to develop eating disorders, such as anorexia, bulimia, and binge eating[14]. Moreover, nonclinical binge eating behavior is very common among the adolescent population, as every weekend a high percentage of this age group engages in episodes of excessive intake of fast food combined with the consumption of large amounts of alcohol and other substances of abuse. The adolescent brain works in a promotivational state, with a strong, fully developed reward system, but still developing inhibitory control areas, such as the prefrontal cortex[15]. Although basal levels of synaptic dopamine are lower during adolescence, there is an increase in drug-induced dopamine release during this period [16,17]. As a consequence, teenagers exposed too early to these potent rewards may suffer from an unbalanced brain reward system when they become adults[18,19].

As several studies have reported that drug use early on in life often predicts an increased likelihood of continued use into adulthood[20], a gateway theory has also been applied to eating disorders[21]. According to the theory, binge eating can lead to the development of another maladaptive behavior, such as drug abuse. The literature available to date points to the mutual influence of palatable diets and psychostimulants, but there is a need to increase awareness of the problem and to perform more studies in humans to confirm the data obtained in preclinical studies.

COMMONALITIES BETWEEN BINGE EATING DISORDER AND DRUG ADDICTION

Behavioral commonalities between binge eating disorder and substance use disorder

The interaction between drug abuse and food, hunger, and appetite, has not inspired interest only in recent times. Since the earliest recorded use of cocaine, indigenous peoples have consumed the drug in order to boost energy levels that allow them to work at high altitude and also to reduce appetite[22]. When cocaine consumption spread to other cultures, cocaine abusers in the United States would report forgetting to eat on many occasions, and had multiple nutritional deficiencies, anorexia and weight loss. Similar observations have been made with respect to methamphetamine, amphetamine, and ecstasy consumers. Under these circumstances, psychostimulants and food compete, and drugs would seem to be the winner[6]. Moreover, although psychostimulants like cocaine or amphetamine produce few withdrawal symptoms, they lead to multiple alterations in appetite and mood[23].

Among eating disorders, binge eating is highly prevalent. The DSM-5 defines binge eating as recurring episodes of rapid and excessive food consumption in a short period of time, marked by feelings of lack of control, and not necessarily driven by hunger or metabolic need[24]. Although binge eating is related to obesity, many people who binge are not obese, and most obese people do not present binge eating disorder[25].

Binge eating and substance use disorders belong to the family of intermittent excessive behaviors, which are associated with loss of control and are clinically comorbid[26,27]. Forms of psychostimulant consumption vary considerably among individuals, with the appearance of a binge pattern being very frequent. Binges or "runs" are defined as the way cocaine is consumed in an intense and repetitive manner over several hours and days[28]. This pattern of cocaine intake is associated with increased medical and psychiatric consequences and is linked to worse health and social outcomes[29,30].

To date, research has revealed a high comorbidity between binge eating and substance use disorders[31], which complicates the evaluation and treatment of both disorders[32] and increases low adherence to treatment[33,34]. An early study at the Center for Addiction and Substance Abuse of the University of Columbia[35] reported that the prevalence of drug abuse was 50% in the case of individuals suffering from eating disorders, while it was around 9% in the general population. On the other hand, 35% of people diagnosed with a substance use disorder exhibited comorbidity with eating disorders, compared with 1%-3% of the general population. More recently, a study performed by an Addictive Behavior Treatment Unit in Spain demonstrated a higher prevalence of eating disorders in a population with substance use disorder[36]. Participants who presented with a substance use disorder had higher scores on all scales indicating the presence of an eating disorder, with values proving especially high in women. A recent study in a university sample showed that binge eating and fat intake were positively related to binge drinking in students[37].

Current research is focused on the symptomatic and neurobiological similarity between alterations in appetite and satiety, obsessive and impulsive disorders, self-destructive behaviors and medical consequences[38]. Among the shared characteristics, several drug addiction symptoms were also observed in individuals with a binge eating disorder[39,40]. Consuming drugs or eating palatable food are both motivated appetitive behaviors with common aspects, and both can evolve into addictive behavior[41]. Both eating disorders and drug abuse commonly begin during a vulnerable period, such as adolescence. In the same way as an individual with a drug addiction ignores responsibilities or obligations in order to take drugs, people with a binge eating disorder devote all their energy to bingeing, purging, exercising, and making efforts to lose weight[42]. Similar to drug abuse, individuals engage in eating disorders despite the serious consequences of the acts in question, making them vulnerable to relapse after periods of regular behavior[43].

Common neurobiology: The dopaminergic, opioid and cannabinoid systems

The brain reward system is clearly the most important neurotransmitter system involved in binge eating and substance use disorders, which are characterized by the impulsive and compulsive intake of drugs or highly palatable food[44,45]. Although multiple neurotransmitters are implicated, the dopamine and opioid systems are the main regulators of feeding behaviors and drug addiction[44,46]. While dopamine is involved in the motivation toward a rewarding activity and its subsequent conditioning, opioids participate in the enjoyment and pleasurable effects of the rewarding activity[47,48]. However, the two pathways do not function independently, and both can be altered by other neurotransmitters[47]. For example, dopaminergic signals can be modified by endogenous opioids, while opioid signaling needs a dopamine D2 receptor to work correctly. In line with this, Smith and Robbins[49] reported that both substance use disorders and binge eating disorder are related by dysfunctional dopaminergic and opioid signaling as well as decreased activity in the prefrontal cortex area, a brain area associated with inhibitory control and decision making. Other studies have found common polymorphisms in the mu-opioid receptor gene and the D2 receptor gene in a sample of individuals with binge eating and substance use disorders, and it has been proposed that the polymorphisms increase vulnerability to the rewarding effects of food and drugs[47,50].

The predisposition to emotion-based impulsive actions observed in both binge eating disorder and substance use disorders[51] can also be explained by neurobiology. Every time an individual takes a drug there is a massive dopamine release that results in a pronounced subjective perception of reward[52]. This experience leads the individual to choose this option to regulate their positive or negative emotional state. Over time, drug use induces changes in neuroplasticity that increase the brain's reward threshold, so that the user requires more drug more frequently to achieve the same pleasurable effects[53]. At this stage, the brain produces neuroadaptations; the effectiveness of dopamine D2 receptors decreases, which is accompanied by a reduced sensitivity to the rewarding effects of other natural reinforcers[54]. These decreased striatal dopamine D2 receptor levels are present in humans with substance use disorder and in animal models of compulsive drug intake

[55].

Regarding binge eating disorder, research shows that women with bulimia nervosa tend to have lower levels of dopamine receptors, and a negative correlation has been highlighted between episodes of binge eating, purging, and striatal dopamine response[56]. Similar to that seen with drugs of abuse, increasingly higher amounts of dopamine need to be released to obtain the same pleasurable effect of palatable food [57]. A decrease in dopamine D2 receptors in the striatum and nucleus accumbens has been described in rats bingeing on sugar[58]. Similarly, after 30 d of intermittent access to a high-sugar beverage, a decrease in dopamine D2 receptors and an increase in dopamine D1 receptors in the dorsal striatum and nucleus accumbens have been described in the same species[59]. Alterations in D2 regulation are related with compulsive drug abuse and binge eating in rodents, with a shift from reward-directed consumption to a compulsive drug and food intake[60,61]. On the other hand, studies in humans have reported alterations in dopamine turnover and receptors in individuals with binge eating disorder[7,62].

Endogenous opioids play an important role in the positive experience associated with eating, both in humans and in animals[63]. Activation of the mu-opioid receptor increases dopamine release in the nucleus accumbens by inhibiting GABAergic neurons in the ventral tegmental area[64,65]. Normally, these neurons provide a tonic-like inhibition of dopamine neurons, but inhibiting this process results in an increase in dopamine release[66]. Studies to date have shown how nutritional conditions can significantly dysregulate the function of the endogenous opioid system, contributing to a worsening of different eating disorders, including binge eating disorder. In fact, some eating disorders have been shown to modify plasma beta-endorphin levels and induce alterations in mu-receptor function[67,68]. We have recently reported decreased gene expression of the mu-opioid receptor in the nucleus accumbens of animals that binged on fat[69]. As an example of the important role that opioids play in binge eating, medications like naltrexone, an opioid antagonist used to treat substance use disorders, work by reducing the frequency of binge eating and purging in bulimia nervosa, and through the positive perception of highly palatable foods[70].

Lastly, a promising therapeutic target is the endocannabinoid system, which is a key point of the regulatory network that controls energy homeostasis[71]. While the opioid is dopamine-anticipating food, the endocannabinoid system is related to the homeostatic control of intake and positive feedback of the specific intake of fatty food [72]. Hypothalamic endocannabinoids control food intake by decreasing satiety signals and increasing orexigenic signals[73]. Moreover, they modulate reward mechanisms by interacting with the mesolimbic pathways, increasing the motivation to eat and possibly reinforcing the incentive or hedonic value of food[74]. Some studies have discovered alterations in anandamide, an endogenous cannabinoid ligand, in patients with anorexia and binge eating disorder, but not in those with bulimia nervosa, suggesting a possible involvement of endocannabinoids in the rewarding aspects of aberrant eating behaviors[75]. Recent animal studies have highlighted changes in brain levels of anandamide in rats that binge on fat[76] and changes in *CB1r* gene expression in the prefrontal cortex and nucleus accumbens[69]. The neurobiological relationship between substance use disorders and binge eating disorder is shown in Figure 1.

ANIMAL STUDIES: PALATABLE FOOD SENSITIZES TO DRUG ADDICTION

In this section we will review a series of basic studies focused on intermittent and limited access to palatable food, which mimics binge eating disorder and induces an escalation in intake over time. Currently, there is evidence that the composition of a diet, such as the percentage of sugar or fat, can affect the intake of drugs of abuse. Laboratory animal models are useful for understanding the factors that contribute to both disorders, helping to broaden horizons and open new perspectives of treatment [42]. As we have previously explained, psychological and biological similarities between palatable food intake and addiction to drugs of abuse have previously been reported, highlighting common reward mechanisms and suggesting that nutritional status is an important factor in the development of addiction[7].

Some authors have implied that, rather than the food itself, it is the way food is consumed that alters the reward system and contributes to vulnerability to other addictive disorders[77,78]. Current research mainly concentrates on two animal eating patterns that modulate reward system function, continuous access *vs* limited access models. While continuous ad libitum access to palatable diets creates animal models of obesity and metabolic syndrome, the limited access model resembles binge eating in

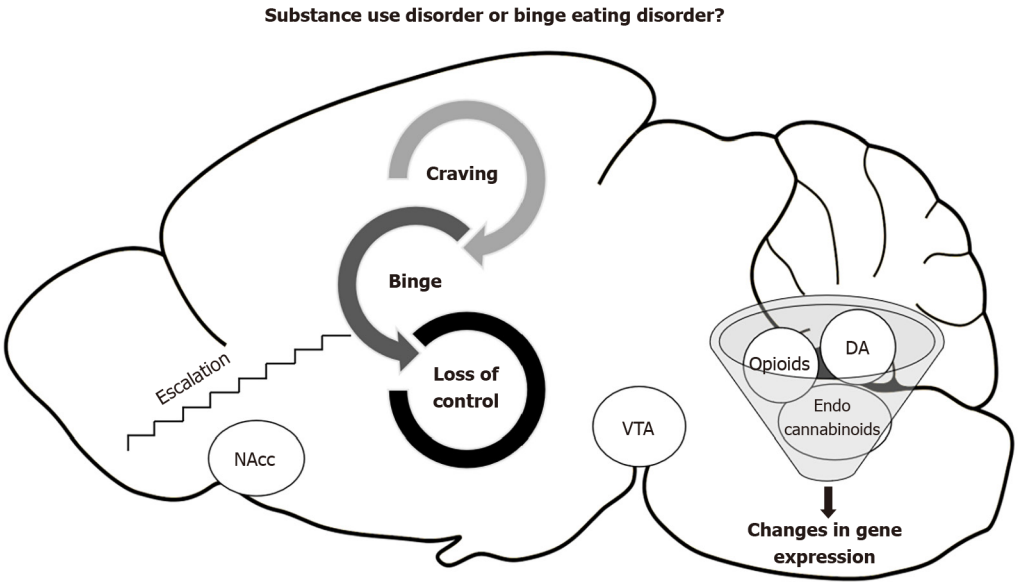


Figure 1 Relationship between substance use disorders and binge eating disorder. DA: Dopamine; NAcc: Nucleus accumbens; VTA: Ventral tegmental area.

its intermittent pattern[78]. Although animal models of binge eating reveal behaviors similar to those seen in humans, they mimic only some of the characteristics of the human disorder. They do not include blame, guilt, the sense of losing control, or the social influence of human eating behavior[79]. Despite these limitations, they share numerous features with human patterns of eating; for example, animals ingest a large amount of food in a brief period of time, exceeding the quantity that an animal maintained on a standard diet would eat in similar circumstances[80].

There are three binge eating models that have been the most widely used to date. The model of sugar bingeing proposed by Avena[58] was the first animal model of food addiction. In that model, animals have intermittent access to a 10% sugar beverage and develop behaviors and brain changes that are analogous to those produced by drugs of abuse in addition to a withdrawal syndrome similar to that induced by opioids. Artiga *et al*[81] described another model, a history of dieting and stress that induces binge eating behavior with palatable and nonpalatable foods. In that model, rats are subjected to cycles of food restriction and refeeding. For 5 d, they are administered only 66% of the standard diet given to control animals. For the next 2 d, animals have ad libitum access to chow and chocolate cookies, *etc.* The repetitive cycle is a good model to mimic what occurs in disorders like bulimia nervosa, as a prior history of energy deprivation is the most critical trigger of binge eating. The third program is the limited access model of Corwin *et al*[82]. It is a non-food-deprivation model in which rats have sporadic, intermittent, and limited access to high-fat food that allows an escalation of food intake to occur[83]. Eating in the absence of hunger is one of the most important characteristics of binge eating in humans, which demonstrates its hedonic nature[80,84].

Research on the link between binge eating disorder and vulnerability to drug addiction points to two main behavioral outcomes, cross-sensitization and the gateway theory[85]. The cross-sensitization phenomenon refers to the effects of bingeing on palatable foods, which leads to long-lasting neuroadaptations that increase the acute response to another drug. Early research in this area focused on the locomotor response to different drugs of abuse after exposure to different binge eating patterns. The majority of studies showed that animals developed a pattern of bingeing on palatable food, and exhibited enhanced locomotor sensitization to amphetamine[86,87] and cocaine[88-90]. These initial studies indicated that the compulsive behavior of bingeing on palatable food sensitizes the same system on which psychostimulants exert their action[86]. Intermittent access to palatable food promptly promotes a compulsion in intake and stimulation of the dopamine circuits in the nucleus accumbens that is sustained over time[62]. The response of the nucleus accumbens is similar to that observed after consumption of psychostimulants. Initially, when food is novel and palatable, dopamine levels in the shell increase, while those in the core are released independently of the reward's novelty[91]. Avena *et al*[77] suggested that

dopamine release derived from bingeing on palatable food is not subject to habituation, as it remains elevated even after repeated bingeing episodes.

After having shown that binge eating behavior induces increased sensitivity to the locomotor effects of psychostimulants, subsequent studies went further and investigated whether animals were also more prone to develop a substance use disorder, such as an increase in cocaine seeking and consuming. Most studies used operant self-administration (SA) and conditioning place preference (CPP) paradigms. The SA paradigm directly assesses a mouse's disposition to take the drug, as animals have to press a lever to experience the drug's rewarding effect. The animal is free to choose to consume or not, and the paradigm directly measures motivation for the drug[92]. On the other hand, the CPP focuses on the role of contextual cues associated with the pleasurable effect of the drug. Mice associate a place or compartment with the rewarding experience of the drug and eventually develop a conditioned preference for that place[93]. Both paradigms provide a complete picture of what occurs in human addiction, when people consume to enjoy the pleasurable effects of the drug, but also because they find themselves in certain social contexts. These aspects play a crucial role in relapse into drug seeking.

To evaluate whether bingeing on palatable food alters an animal's disposition and motivation to take a drug, a 2011 study that used the limited access model of Corwin found a tendency toward an increase in intravenous cocaine SA, but the effect was not significant[94]. Consequently, we performed several mouse studies in our laboratory to further investigate this phenomenon, confirming that bingeing on fat during an early period of life, such as adolescence, enhanced intravenous cocaine SA and motivation to obtain the drug in adulthood[69]. We also used Corwin's limited access model, in which adolescent mice had limited access to a high-fat chow for 2 h, 3 d/wk, with continuous access to a standard diet in their home cages. We observed an escalation in the intake of fat from the second week onwards, which confirmed the rapid development of fat bingeing behavior. Mice exposed to the high-fat binge sessions during adolescence showed an increase in cocaine SA compared with those fed a healthy standard diet. After acquiring a sustained cocaine SA, animals under-went an extinction process. When the operant behavior of pressing the lever to obtain cocaine was extinguished, mice were exposed once again to a single high-fat binge, which induced a strong reinstatement of the cocaine SA. Similarly, Barnea *et al*[85] observed that restricted access to a palatable diet was a risk factor for cocaine SA and drug craving and for binge eating state and trait, especially in the latter case. A binge eating state is induced by intermittent access to palatable diets, while the binge eating trait is a phenotypical proneness for overeating.

Regarding the key role of environmental clues in psychostimulant reward, a series of studies was performed in which animals that binged on fat during adolescence developed CPP for the drug-paired compartment, even with very low doses of cocaine [69] that were not effective in animals on a standard diet. The results confirmed that bingeing on fat increases sensitivity to the rewarding effects of cocaine and strengthens contextual memories associated with the pleasant experience.

Finally, palatable food can also induce withdrawal or craving for specific kinds of foods that are generally high in fat, salt, and sugar, much like that observed in drug addiction. For example, patients have described intense feelings of panic and anxiety when they are forced to postpone a binge eating episode or when they remove certain types of palatable food from their diet, leading to headaches, irritability, and anxiety [56,95]. Studies in animals also confirm that withdrawal symptoms are experienced when binge eating of specific kinds of food is stopped, confirming its potent effect on the brain[69,96,97]. The withdrawal-like symptoms common to cessation of any palatable diet arise following an increase in corticosterone and anxiety levels[98-100].

The effects of cessation of palatable food bingeing on the reward system have also been studied. For example, there is a significant increase in the locomotor response to cocaine after withdrawal from sugar[88,101]. Furthermore, animals that stop bingeing on fat are more resistant to forgetting the contextual memories associated with cocaine, and are more liable to relapse after lower cocaine doses[69]. All the studies suggest that bingeing on palatable food not only increases sensitivity to the rewarding effects of cocaine, but also heightens vulnerability to relapse into drug seeking.

CONCLUSION

Based on the literature published to date, we can conclude that the relationship between binge eating disorder and substance use disorders is a two-way street. On one

hand, binge eating can be a risk factor or a gateway to drug addiction, and on the other, psychostimulant addiction can lead to several eating disorders. While we have referred to binge eating disorder throughout the review, binge eating may produce the same effects without necessarily meeting the diagnostic criteria for binge eating. In the same way as substance abuse, binge eating interferes with daily life and is characterized by persistence of the behavior despite the associated negative consequences, which include guilt, stress, and compensatory behaviors[6]. In relation to the binge cycle, an important common factor between eating disorders and drug abuse is relapse. Nair and colleagues[102] described how, on many occasions, people decide to diet and exercise, but that the resolve only lasts a few weeks, with a rapid return (relapse) of old (bad) habits. In that way, dieting induces changes in the reward system that can subsequently result in relapse into binge eating episodes and overeating.

In this review we have drawn a picture of bingeing on palatable food as something that is as harmful as substance abuse. If feeding is a risk factor that affects the same neurobiological mechanisms as drugs of abuse, early exposure to certain types of ultraprocessed food could be a gateway to increased sensitivity to reward. The high comorbidity that exists between the two disorders supports the hypothesis and highlights the importance of identifying and treating both conditions.

In the same manner that clinicians observe multiple nutritional deficiencies, anorexia and weight loss in cocaine abusers, which is described at the beginning of the review, the opposite effect can be observed after drug withdrawal[103]. Overeating during the rehabilitation phase is often recommended as part of detoxification programs as a way of counteracting craving. In this context, the concept of "addiction transfer," where one addiction is replaced by another, has been proposed[104]. Indeed, increase in the rate of obesity among patients undergoing detoxification can be so dramatic that current substance addiction programs are beginning to complement treatment with physical exercise and diet programs to avoid it.

Most professionals focus on their area of expertise, resulting in the vital need for integrated services to deal with dually diagnosed patients who have a complex profile because of their substance use and binge eating disorders[105]. Until now, there have been no guidelines for experts to treat this comorbid condition. It is surprising that most specialists in substance abuse centers do not follow protocols that broach eating disorders among their patients. Likewise, most clinicians dealing with eating disorders are not trained to detect or investigate the possible misuse of substances of abuse.

Nutritional patterns should be considered an important variable in the treatment of people with substance use disorder, as an eating disorder may develop in parallel to detoxification from the drug, consequently affecting social relationships, cognitive functions, and lifestyle. Future studies should focus on specific treatments and interventions for individuals who have a special vulnerability to transfer from one addiction to another. It is now necessary to discover new therapeutic targets of food and drugs in order to improve public health solutions. In this context, new nutritional interventions are the focus of increasing investigation as possible modulators of reward and other diseases.

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World J Psychiatr 2021 September 19; 11(9): 530-542

DOI: 10.5498/wjp.v11.i9.530

ISSN 2220-3206 (online)

MINIREVIEWS

Genetics of adult attachment: An updated review of the literature

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Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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Abstract

Attachment style, which has been theorized to be rooted in childhood bonding experiences, influences adult cognitive, emotional and interpersonal functioning. Despite its relationship with early experiences, research indicates that the continuity of attachment style across childhood and adulthood is only partial,

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: April 21, 2021
Revised: May 4, 2021
Accepted: July 29, 2021
Article in press: July 29, 2021
Published online: September 19, 2021

P-Reviewer: Arumugam VA, Miwa T, Zhang XQ
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Guo X

being a malleable tendency that is shaped throughout development, with an increasing influence of genetics, as it occurs in other cognitive and behavioral phenotypes. Genetic research indicates that up to 45% of the variability in anxious and 39% in avoidant adult attachment style could be explained by genetic causes, but the precise mechanisms remain unclear. A narrative review is conducted analyzing the existing literature regarding the implication of candidate genes related to oxytocin, dopaminergic pathways, serotonergic pathways and brain-derived neurotrophic factor in adult attachment, with both vulnerability and differential susceptibility approaches, yielding mixed results. We highlight the lack of genome-wide studies and the scarcity of epigenetic investigation. Based on the existing data, we conclude that the genetics of adult attachment is an area that requires further research to clarify its etiological role and that it should be preferably approached as an interaction between nature and nurture.

Key Words: Genetics; Adult attachment; Oxytocin; Dopamine; Serotonin; Brain-derived neurotrophic factor; Methylation

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Core Tip: Attachment style influences adult cognitive, emotional and interpersonal functioning. Despite its relationship with early experiences, it is a malleable tendency that is shaped throughout development. Genetic research indicates that up to 45% of the variability in anxious and 39% in avoidant adult attachment style could be explained by genetic causes. A narrative review is conducted analyzing the existing literature regarding the implication of candidate genes, with vulnerability and differential susceptibility approaches. We highlight the lack of genome-wide studies and scarcity of epigenetic investigation, concluding that further research is needed to clarify the etiological role of genetics on adult attachment.

Citation: Erkoreka L, Zumarraga M, Arrue A, Zamalloa MI, Arnaiz A, Olivas O, Moreno-Calle T, Saez E, Garcia J, Marin E, Varela N, Gonzalez-Pinto A, Basterreche N. Genetics of adult attachment: An updated review of the literature. *World J Psychiatr* 2021; 11(9): 530-542
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/530.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.530

INTRODUCTION

Attachment has been defined as the tendency of human beings to create strong affective bonds towards specific figures and explains the various forms of emotional stress and personality pathology, including anxiety, anger, depression and emotional detachment, that result from unwanted separation or loss of such figures[1]. During childhood, the relationship with the parent is the primary attachment, and this will be gradually replaced, during adolescence and adulthood, by social and romantic relationships.

Broadly speaking, the type of attachment can be defined as secure or insecure. Different proposals describe distinct types of insecure attachment, as we will detail below, although the most widely used is the two-dimensional one that distinguishes anxious and avoidant attachment styles. Secure attachment is seen as an internal resource that allows for the management of negative emotions and the recovery of calm, as well as a source of resilience. In contrast, an insecure attachment style facilitates the development of psychological distress and eventual psychopathology [2]. It has been shown that the attachment style plays a determining role in cognitive, emotional and social-interactional aspects of the individual.

ATTACHMENT STYLES

The concept of attachment style was first proposed by Ainsworth in the 1970s to

describe children's response patterns to separation from their mothers during the Strange Situation Procedure, designed to assess attachment pattern[3]. Children were described as secure if they showed separation distress and sought contact and calmed down with the mother after the reunion. On the other hand, children were classified as insecure-avoidant if they showed little separation distress and avoided contact with their mother after the reunion. Finally, insecure-ambivalent/resistant children were those who showed extreme distress before separation and ambivalent behaviors after the meeting with the mother. It has been proposed that deactivation of the attachment system occurs in avoidant children and hyperactivation in ambivalent/resistant children. Later, Main and Solomon[4] added the disorganized attachment style to describe those children who did not present coherent attachment strategies, oscillating between different types or presenting bizarre behavior after the reunion.

Beginning in the 1980s, several researchers developed new measures to assess attachment style in order to extend the study to adolescents and adults. Maintaining a developmental perspective, George *et al*[5] developed the Adult Attachment Interview (AAI), which assessed the mental representations of attachment (or states of mind in relation to attachment) towards the parents in relation to childhood. Through this interview, the attachment style was classified as secure, dismissing, preoccupied or unresolved/disorganized[5].

In the same period, Hazan and Shaver[6] developed a self-administered questionnaire to assess attachment in adult relationships, and based on Ainsworth's styles, the individual was classified as secure, avoidant or anxious/ambivalent[6]. With a similar focus, Bartholomew and Horowitz[7] developed another proposal, in which attachment was also assessed by means of a self-administered questionnaire and classified as secure, dismissive, preoccupied or fearful. It gradually became evident that adult attachment could be assessed along two main dimensions: Anxiety and avoidance[8]. Anxiety explores concern regarding the availability and responsiveness of the other, and avoidance, on the other hand, evaluates interindividual differences regarding the degree of comfort with closeness and interdependence. It has been proposed that low scores on both anxiety and avoidance are suggestive of secure attachment; high scores on anxiety alone would indicate an anxious type of insecure attachment; high scores on avoidance alone would indicate an avoidant type of insecure attachment; and high scores on both dimensions would be suggestive of disorganized attachment, although a solely dimensional treatment of the two variables is recommended[2].

STABILITY AND CHANGE OF THE ATTACHMENT SYSTEM

Adult attachment research, therefore, has been conducted using the two aforementioned models. The first is based on the AAI, a semi-structured interview that explores the adult's current state of mind and the coherence of discourse in relation to childhood attachment experiences, and the second is based on the evaluation through self-administered questionnaires of beliefs and experiences related to attachment in the adult's current relationships with significant others. Nevertheless, although both maintain the same theoretical background, divergences have been found in the results obtained between the two models, with correlations interpreted as trivial to small[9]. These results suggest that there is no significant equivalence between attachment measured with the AAI, more focused on childhood experiences, and that assessed with self-administered questionnaires in relation to current significant figures.

A lack of continuity has also been observed even between childhood attachment and that assessed in adults using the AAI or equivalents, despite the fact that both assess the quality and style of the relationship with the parents during childhood. A meta-analysis concluded that the overall stability in the type of attachment assessed by the Strange Situation Procedure (or equivalents) in childhood and by the AAI (or equivalents) in adulthood was 0.39, which is interpreted as medium-sized stability. However, there was no significant stability for intervals longer than 15 years. Interestingly, and in relation to subgroups with psychosocial risks, it was observed that securely attached children that belonged to these groups were less likely to maintain attachment security, whereas insecurely attached children were most likely to maintain insecurity[10].

These results suggest the existence of other variables that would act throughout development and that would intervene in the shaping of adult attachment. In this sense, it has been described that in addition to the relationship with caregivers in childhood, emerging social competence (the socialization skills of children assessed by

their teachers at school) and the quality of the relationship with best friends in childhood-adolescence independently and significantly influence adult attachment style[11].

Working models of attachment formed in infancy are sensorimotor, procedural and nonlinguistic in nature, reflecting interactions between the infant and caregiver that occurred prior to the emergence of linguistic and introspective abilities. Thus, different theorists have contributed to the development of a "prototype" theory that posits the coexistence of current working models and early prototypical models. Prototypical working models formed during early life would continue to exist and exert a shaping effect on attachment patterns throughout life, both by attempting to match new experiences to pre-existing models and by reinforcing them through behaviors that elicit reactions consistent with the individual's expectations. In addition, current ones would be revised and updated as relevant attachment experiences arise that differ from, or challenge, previous experiences and knowledge (such as the loss of an attachment figure or infidelities), thus enabling and explaining variations in attachment style across the lifespan[2]. In the same line, other authors also describe that children's attachment patterns are malleable and shaped by multiple experiences in the transition to adulthood, pointing out that socialization and selection effects have a differential influence according to the life stage[12].

ADULT ATTACHMENT AND PERSONALITY

The relationship between attachment style and personality is also an aspect to be considered in this area of investigation. Although attachment research tends not to emphasize the temperamental contribution to attachment styles, Bowlby[13] himself suggested that there may be preexisting temperamental differences in children and that attachment experiences would modulate, interact with or overcome these differences. In this line, several authors have described a certain degree of overlap in the heritability of personality features and attachment styles in studies carried out using self-administered questionnaires to explore adult attachment[14-16]. It has been reported that 63% of the association between attachment anxiety and personality dimensions was attributable to common genetic effects[14]. Other authors described that genetic influence on neuroticism contributed to 35% of the variance in anxiety and 11% in avoidance, whereas genetic influence on extraversion contributed to 6% of the variance in avoidance[15].

In a study conducted by our group with a general population sample, we found that a functional polymorphism in the catechol-o-methyltransferase (COMT) gene had a common influence on avoidant attachment and inhibitedness personality dimension. This was not due to a poor discriminative capacity of the instruments, since independent associations were observed, for example, between a polymorphism in the serotonin transporter (5HTT) gene and both variables[16].

In this regard, it has been proposed that temperamental characteristics, which are strongly influenced by genetics, would influence internal working models of attachment in complex ways, including person-environment interaction and gene-environment interaction[15]. In addition to the genetic conditioning that may exist, and that will constitute the temperamental basis by which the individual tends to experience certain affects in his or her experience of the other, starting from primary object relations, there is a continuous and close interaction between personality and attachment style throughout development. It will determine the social choices and the way in which the individual perceives relationships throughout life. The greater capacity of the adult to make these social decisions, determined in part by temperamental aspects, could explain to some degree the discrepancies observed between samples of children and adults in genetic research of attachment, which are detailed below.

GENETICS OF ADULT ATTACHMENT

Methods

A literature search was performed to identify studies on genetics of adult attachment. Articles published until December 28, 2020 were retrieved from the PubMed database using broad search terms in order to identify as many potentially eligible studies as possible: [(attachment OR "adult attachment") AND (genetic* OR dopamine* OR

COMT OR serotonin* OR oxytocin* OR brain-derived OR BDNF)]. An age filter was added: "Adults: 19+ years". The reference lists of the selected studies and reviews were also checked to identify additional relevant articles using a snowballing approach. Studies were included if: (1) They investigated the influence of genetics/epigenetics on adult attachment using any approach (twin-studies, genome-wide studies or candidate gene studies); (2) They used standard measures of adult attachment (AAI or self-administered questionnaires); (3) They were systematic reviews, meta-analyses, narrative reviews or original research studies; and (4) They were written in English or Spanish.

This is not a systematic review but a narrative one; it summarizes the findings described in the selected reports and, in this way, provides an overview on the subject.

Heritability of attachment: Twin-studies

In twin-studies of children, the combination of shared and nonshared environmental variables seems to explain most of the variability in attachment style, with no significant weight of genetics observed[17-19]. Shared environmental factors have been described as the environmental influences responsible for resemblance between family members, and nonshared environmental factors as those influences that contribute to differences between family members[20].

In contrast to what has been observed in children, independent twin studies in adolescents and adults describe that attachment is mainly conditioned by genetic and nonshared environmental factors[14,15,21-24]. The only study of adolescent twins to date was conducted using the Child Attachment Interview, a childhood adaptation of the AAI that explores coherence of discourse and childhood attachment experiences in relation to parents. They found that genetic effects accounted for 35% of the variance in attachment security and that the remaining 65% was estimated to be due to the nonshared environment[22].

Most of the twin-studies in adults have been conducted using self-reported questionnaires, but the results are generally similar to those obtained in the adolescent study. The heritability of anxious attachment has been described to be between 37% and 40% in two different studies, the rest being explained by nonshared environmental factors[14,21]. These two groups did not observe avoidant attachment to be explained by genetics. In other studies, however, the heritability of anxious attachment was replicated, and genetic influence was also described for the avoidant style. Additive genetic effects were described to account for 45% of the variability in anxiety and 39% in avoidance in the Michigan State University Twin Study of Behavioral Adjustment[15]. These figures were similar to those obtained in another study, where genetic effects accounted for 45% of individual differences in anxiety and 36% in avoidant attachment[23]. The only report exploring attachment with the AAI in adult twins described that attachment styles were determined by genetics and shared environment[24]; nonetheless, it was a pilot study with a limited sample size.

The differences in heritability observed between studies carried out with samples of children and adult samples are consistent with the lack of stability in attachment style described in longitudinal studies, as we have previously mentioned. They could be due to the way the exploration of attachment is operationalized depending on age; whereas in children it is based on differences in observed attachment behaviors, in adults it is focused on the way individuals think about their attachment relations, in relation to their parents (with the AAI) or in relation to their current close relationships (with self-administered questionnaires).

In addition, age-related increases in genetic influences on various cognitive, behavioral and psychiatric phenotypes have been well-documented, some authors suggesting that shared environmental effects may be relatively restricted to infancy and, when present, may not be stable beyond childhood[25]. The influence of the environment would decrease with age, as the children undergo a variety of influences outside the family, and are more able to shape their own environments[26]. In this line, an increasing influence of genetics has also been observed in relation to affiliation with peers in a relatively short range of years, concretely in the transition from adolescence to adulthood (between the ages of 15 and 21)[27].

Genome-wide association studies

The first genome-wide association study (GWAS) on attachment patterns was conducted in children, providing evidence of novel genes (HDAC1, ZNF675, BSCD1) associated with attachment disorganization[28], but these findings have not been replicated. A subsequent epigenome-wide association study reported that infant attachment was also significantly associated with a principal component that

accounted for 11.9% of the variation in genome-wide DNA methylation[29]. Methylation is associated with lower levels of transcription of a gene when it occurs in the promoter region. The observed effects were most apparent when comparing children with a secure *vs* a disorganized attachment style, and most pronounced in females, providing preliminary evidence for a molecular signature of infant attachment. The complexity of child attachment assessment makes it difficult to conduct studies that involve the analysis of the whole genome and thus require large samples, being the samples of both studies of limited size (samples sizes of 657 and 226, respectively) compared to others of this type. To date, no GWAS on adult attachment have been published.

Candidate gene studies

The bulk of research in adult attachment genetics has been conducted based on a candidate gene approach and has mainly involved polymorphisms in the oxytocin receptor (OXTR) gene and in those involved in dopaminergic and serotonergic pathways, although more recent work has also studied brain-derived neurotrophic factor (BDNF). Candidate gene studies have been conducted reporting either direct associations or gene-by-environment interactions (known respectively as vulnerability and plasticity genes, see Belsky *et al*[30]). We will describe the main findings using both approaches. The findings are summarized in Table 1.

OXTR: Oxytocin (OXT) is a neuropeptide synthesized in the hypothalamus whose known role in the periphery is as an initiator of childbirth and lactation. It also has a central role in social and emotional behavior, insofar as it participates in the formation of emotional bonds across the lifespan[31]. In fact, OXTR are concentrated in brain regions involved in social behavior, including the olfactory processing regions, limbic brain structures, hippocampus, hypothalamus and brainstem[32].

Plasma concentrations of OXT and genetic polymorphisms that involve OTX action, mainly the OXTR gene, have been studied in relation to different aspects of socialization in animals and humans, including attachment. OXTR gene is located on the short arm of chromosome 3 (3p25) and has three introns and four exons. Several dozens of single-nucleotide polymorphisms (SNP) have been identified in the OXTR gene region[33]; among them, rs53576 and rs2254298, located in intron 3, are the most extensively studied in relation to social behavior. In both cases, they consist of mutations in which a guanine (G) base is replaced by an adenine (A) base.

The functionality of these polymorphisms remains unclear[34]. They do not change the amino acid sequence of the encoded protein, and thus it has been proposed that they should exert their effects through variations in brain structure and function[35]. The A allele of rs53576 has been associated with morphometric and functional alterations in hypothalamus and amygdala that predicted lower levels of reward dependence[36]. The rs2254298 OXTR A allele has been associated with larger amygdala volume in different populations[37,38]. These studies provide evidence of a possible convergent impact of OXTR polymorphisms on this key limbic structure.

In relation to adult attachment, an association of the GG genotype of rs53576 with greater insecurity according to self-administered questionnaires has been described [39], and conversely, that this genotype is associated with lower anxiety and avoidance [40]. With regard to rs2254298, the GG genotype has been associated with greater avoidance[39] and lower anxiety[41], the latter in women. Other authors, however, have not found significant associations between these two polymorphisms and attachment styles[11,42,43].

Further, it has been described that rs53576 acts as a moderator in the continuity of secure attachment from childhood to adulthood, so that in those individuals with the GG genotype, infant attachment security predicted romantic attachment security in adulthood[44].

Finally, when we study the interaction of the OXTR gene genotypes with environmental variables, a role in the intergenerational transmission of attachment, in interaction with childrearing style, has been reported[45], whereas other authors have not found any interaction with parental sensitivity[11]. Recent epigenetic studies coincide in describing that the higher the methylation in the promoter region of the OXTR gene, the higher the avoidant attachment score[46,47]. These studies have been conducted on saliva and peripheral blood samples, respectively.

Dopaminergic system: Regarding the dopaminergic pathway, the genes of the dopaminergic receptors D2 (DRD2) and D4 (DRD4) and of the COMT have been mainly studied.

Table 1 Summary of candidate gene studies on adult attachment

Gene	Marker	Ref.	Adult attachment measure	Result
OXTR	rs53576	Costa *et al*[39], 2009	ASQ	GG greater insecurity
		Monin *et al*[39], 2019	ECR	GG lower anxiety and avoidance
		Raby *et al*[44], 2013	CRI	GG predicts continuity of attachment security
		Fraley *et al*[11], 2013	RSQ	No significant associations or interactions with maternal sensitivity
		Gillath *et al*[42], 2008	ECR	No significant associations
		Gong *et al*[43], 2020	RAAS	No significant associations
	rs2254298	Costa *et al*[39], 2009	ASQ	GG higher avoidance
		Chen and Johnson[41], 2012	ECR	GG lower anxiety in females
		Fraley *et al*[11], 2013	ECR	No significant associations or interactions with maternal sensitivity
		Gong *et al*[43], 2020	RAAS	No significant associations
	Methylation promoter region	Ebner *et al*[46], 2019	ECR	Higher methylation associated with higher avoidance
		Ein-Dor *et al*[47], 2018	AAS	Higher methylation associated with higher avoidance
DRD2	rs1800497	Gong *et al*[43], 2020	RAAS	A1 homozygotes higher anxiety than A2 carriers
		Fraley *et al*[11], 2013	ECR	No significant associations or interactions with maternal sensitivity
DRD4	VNTR	Reiner and Spangler[51], 2010	AAI	7R carriers greater security
		Bakermans-Kranenburg *et al*[52], 2011	AAI	7R carriers greater susceptibility to environmental factors
COMT	rs4680	Erkoreka *et al*[16], 2018	ECR	ValMet heterozygotes higher avoidance than either homozygotes
5HT1A	rs6295	Gong *et al*[43], 2020	RAAS	G carriers less comfortable in close relationships
5HT2A	rs6313	Gillath *et al*[42], 2008	ECR	T homozygotes higher avoidance than C homozygotes
		Salo *et al*[62], 2011	RSQ	T homozygotes greater susceptibility to environmental factors
		Fraley *et al*[11], 2013	ECR/RSQ	C homozygotes higher anxiety (RSQ)
5HTTLPR	rs4795541	Caspers *et al*[64], 2009	AAI	Higher unresolved attachment
		Reiner and Spangler[51], 2010	AAI	No significant associations
		Bakermans-Kranenburg *et al*[52], 2011	AAI	No significant associations
		Erkoreka *et al*[16], 2018	ECR	No significant associations
	Methylation promoter region	van IJzendoorn *et al*[65], 2010	AAI	Higher methylation in L homozygotes increased risk or unresolved loss or trauma; higher methylation in S homozygotes less unresolved loss or trauma
		Jones-Mason *et al*[66], 2016	AAI	Methylation interacts with socioeconomic status
BDNF	rs6265	Suzuki *et al*[68], 2012	PBI	Met carriers with low maternal care greater interpersonal sensitivity
		Ibarra *et al*[69], 2014	PBI	Met carriers greater susceptibility to childrearing style

5HT1A: Serotonin receptor A1; 5HT2A: Serotonin receptor A2; 5HTTLPR: Serotonin transporter-linked polymorphic region; AAI: Adult Attachment

Interview; ASQ: Attachment Style Questionnaire; BDNF: Brain-derived neurotrophic factor; COMT: Catechol-o-methyltransferase; CRI: Current Relationship Interview; DRD2: Dopaminergic receptor D2; DRD4: Dopaminergic receptor D4; ECR: Experiences in Close Relationships; OXTR: Oxytocin receptor; PBI: Parental Bonding Instrument; RAAS: Revised Adult Attachment Scale; RSQ: Relationship Questionnaire.

The gene that encodes DRD2 contains a SNP (TaqIA, rs1800497) that gives rise to the A1 allele (when thymine [T] is present) or A2 allele (when cytosine [C] is present). A1 allele is associated with a reduced number of dopamine binding sites in the brain [48]. Individuals with two A1 alleles were found to score higher on attachment anxiety than those with only one, or none A1-alleles[42]. A subsequent study, however, found no relationship between this polymorphism and attachment style, either directly or in interaction with maternal sensitivity[11]. Both studies were carried out with the same self-administered questionnaire, so there was no methodological variability that could explain the differences in results.

The DRD4 gene contains a functional polymorphism consisting on a variable number of tandem repeats, in which a 48 base pair sequence exists as a 2-fold to 10-fold repeat[49]. The 7-repeat (7R) allele has been described to have a reduced ability to inhibit neuronal firing in the prefrontal cortex and thus, proposed to associate higher dopaminergic stimulation at that level[50]. There is an extensive literature on infant attachment and its relationship with this gene; however, only two studies have studied its effect on adult attachment. In both studies, the assessment of attachment style was carried out using the AAI. According to the first study, carriers of the 7R allele were significantly more likely to be securely attached, although this was only true for subjects reporting unloving caregiver recollections[51]. The authors of the second study, on their part, did not find a direct association of the polymorphism with the type of attachment. Instead, they observed that 7R allele carriers showed a heightened susceptibility to environmental influences[52], so that the carriers that reported parental problems had the highest scores for unresolved loss or trauma and the carriers without parental problems had the lowest scores. No differences according to parental problems were found among participants without the 7R allele.

COMT participates in the breakdown of dopamine and noradrenaline. Its gene contains a functional SNP (COMT Val158Met, rs4680), a substitution of G for A, which translates into an exchange of valine (Val) for methionine (Met) in the protein. MetMet homozygote individuals have four times less enzymatic activity than ValVal homozygotes, whereas heterozygotes show an intermediate level of activity. Activity associated with this polymorphism is particularly important in the prefrontal cortex, and it has been associated with numerous psychopathological phenotypes[53].

Individual heterozygous for COMT Val158Met were found to exert a more avoidant attachment pattern than homozygotes for either allele in the general population[16]. The pattern observed, in which heterozygotes scored higher than either homozygote, is called molecular heterosis. One of the explanations proposed for this fact is that on the cellular level, heterozygosity confers a broader range of genetic expressions and provides greater plasticity[54]. Although no previous or latter studies on adults have replicated this finding, they were coherent with previous research conducted in children[55].

Serotonergic system: Regarding the serotonergic system, both serotonin 1A (5HT1A) and 2A (5HT2A) receptor genes and the 5HTT gene have been studied.

Five-5HT1A is one of the most abundantly expressed serotonin receptors in the brain, acting at both pre- and post-synaptic neurons in several brain areas[56]. A SNP (C1019G, rs6295) in the gene has been suggested to regulate the 5HT1A receptor expression in presynaptic raphe neurons[57,58]. Compared with the C allele, the G allele is associated with higher expression in raphe neurons, leading to a decrease in firing frequency and serotonin level in synaptic cleft[57,59]. Individuals with the CG and GG genotypes have been associated with feeling less comfortable in close relationships than individuals with the CC genotype[60].

The gene that encodes 5HT2A contains a functional SNP (T102C, rs6313); the presence of T allele has been associated with reduced serotonin binding in the prefrontal cortex and, thus, with reduced serotonergic activity[61]. Individuals homozygote for T allele were found to score significantly higher on avoidant attachment than those homozygotes for C allele[42]. However, this finding was not replicated in a subsequent study, which reported that homozygotes for C allele scored higher on anxiety than T allele carriers[11]. An interaction of this polymorphism with maternal nurturance in childhood has also been observed, such that high childhood maternal nurturance predicted low avoidant attachment in the TT homozygotes but

not in carriers of C allele, whereas low maternal nurturance was associated with high avoidance in TT homozygotes but not in C allele carriers. It suggests that a gene-environmental interaction exists, with T homozygotes showing a heightened susceptibility to environmental factors[62].

The 5HTT is responsible for the recapture of serotonin from the synaptic cleft. Its gene includes a 44 base pair deletion/insertion polymorphism in the promoter region (5HTTLPR, rs4795541) and is one of the most widely studied genetic variants in psychiatric research. The long (L) allele in the promoter is associated with raised serotonin transporter messenger RNA levels, which translates into elevated transcription activity, greater transporter density and, therefore, serotonin hypofunction. The short (S) allele has the opposite effect, that is, it is associated with lower transcription activity, less transporter density and, therefore, a greater concentration of serotonin in the synapse. Further, the S allele behaves in a dominant manner [63].

An association between the S allele of 5HTTLPR and increased risk for unresolved attachment according to the AAI was described[64], although it has not been replicated. No direct effect of 5HTTLPR on attachment styles has been subsequently found, either assessed with self-report questionnaires[16] or when explored by means of the AAI[51,52].

Two studies examining methylation of the 5HTTLPR have been published so far, both of them exploring attachment styles using the AAI. Higher levels of methylation of 5HTTPR in DNA obtained from peripheral lymphoblasts were described to be associated with an increased risk of unresolved loss or trauma in homozygotes for the L allele. Higher levels of methylation in S allele homozygotes were associated with less unresolved loss or other trauma[65]. More recent research examining methylation of the 5HTTLPR gene in DNA from peripheral lymphocytes, as well as socioeconomic status (SES), concluded that lower methylation and low-SES were associated with higher unresolved loss, and higher methylation and low-SES with higher unresolved trauma. Within the unresolved category, low-SES unresolved participants had higher levels of methylation than mid/upper-SES participants, whereas SES was unrelated to methylation within the secure and organized categories[66]. Although these results require careful analysis, it appears that both gene-environment interaction and epigenetic mechanisms may play a role in the contribution of 5HTTLPR to attachment style.

BDNF: BDNF is one of the proteins of the neurotrophin family. It acts by promoting the survival of existing neurons, contributes to the growth and differentiation of new neurons and synapses and protects against stress-related neuronal damage. The gene encoding BDNF contains a functional SNP-like polymorphism, the BDNF Val66Met (rs6265), in which a G for A base change in the gene results in the substitution of Val for Met in the protein[67]. The presence of Met in the protein is associated with lower concentration of pro-BDNF in dendrites and secretory glands and a lower secretion of the molecule into the synaptic space.

With respect to this polymorphism, a synergistic effect has been described between being a Met carrier and low maternal care according to the Parental Bonding Instrument, leading to a greater interpersonal sensitivity[68]. In another study, Met carriers showed greater sensitivity to the childrearing style, according to the Parental Bonding Instrument, in relation to developing anxiety and somatization in adulthood [69].

CONCLUSION

The evidence about a significant influence of genetics on adult attachment comes mainly from twin-studies, but the specific ways and mechanisms remain unclear. Research has been focused on candidate gene studies, and although some markers such as the rs53576 and rs2254298 polymorphisms in the OXTR gene seemed promising, no consistent results have been found across the studies. The same is true for the described functional polymorphisms affecting dopaminergic and serotonergic systems (in the DRD2, DRD4, COMT, 5HT1A, 5HT2A, 5HTT genes). It should be noted that the only replicated finding is the association between methylation of the promoter region of the OXTR gene and higher attachment avoidance, even using different attachment measures (in both cases, self-reports). Carrying the Met allele in the BDNF rs6265 polymorphism also seems to confer certain vulnerability to environmental factors related to childrearing, although the studies published so far have been conducted with different methodology, making it difficult to compare the results.

Admittedly, the scarcity of data, the methodological differences in relation to the exploration of the adult attachment (AAI *vs* self-administered questionnaires) and the doubts raised about the comparability of data obtained in children (more abundant) and adults make it difficult to draw conclusions regarding the specific contribution of genetics to adult attachment. Different authors propose that the weight of genetics and environment on attachment styles differs in childhood and adulthood, so that during childhood the shared environment would be the main contributor to attachment style, whereas the biological-temperamental and the nonshared environment would acquire greater importance in adulthood[12,26,70]. These differences in the weight of genetics depending on the life stage are not unique to attachment style and have been observed in other cognitive and behavioral phenotypes as well[25,71-73].

In addition, the importance of gene-environment interaction to explain the contribution of genetics to the formation of attachment styles has also been emphasized, suggesting that research should focus more on the search for differential susceptibility or plasticity genes than on direct associations. Epigenetic research, currently in its embryonic stage in the area of attachment, has also been highlighted[26]. The studies exploring differential susceptibility, as well as epigenetic research, are precisely the ones that have yielded the most promising results to date and on which future research should probably be based.

We could therefore conclude that: (1) More research is needed to understand the precise contribution of genetics to adult attachment style; (2) Future research should take into account that the patterns observed in children and adults may differ; and (3) Additional studies should include the study of environmental variables that could affect affiliative behaviors.

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World Journal of Psychiatry

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World J Psychiatr 2021 September 19; 11(9): 543-552

DOI: 10.5498/wjp.v11.i9.543

ISSN 2220-3206 (online)

MINIREVIEWS

Recent advances in the treatment of opioid use disorders–focus on long-acting buprenorphine formulations

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Author contributions: All written by both authors.

Conflict-of-interest statement: There are no conflicts of interest.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Germany

Peer-review report's scientific quality classification

Grade A (Excellent): 0

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Abstract

Oral methadone or sublingual buprenorphine are first-line medications for pharmacotherapy of opioid use disorders (OUDs). Three long-acting buprenorphine depot or implant formulations are currently available for the treatment of OUDs: (1) CAM 2038 (Buvidal) for subcutaneous weekly and monthly application; (2) RBP-6000 (Sublocade™) as a monthly depot formulation; and (3) A six-month buprenorphine implant [Probuphine™]. The pharmacology, clinical efficacy and prospects of these medications are discussed.

Key Words: Opioids; Opioid dependence; Maintenance treatment; Methadone; Buprenorphine; Depot; Implant

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Core Tip: Although opioid maintenance therapy with methadone or buprenorphine is the widely accepted first line treatment in opioid use disorders (OUDs) the risk of diversion and low retention rates limit its use. While previous attempts to introduce long-acting methadone analogues have failed due to cardiac side effects in recent years, three different long-acting buprenorphine formulations have been developed and successfully studied in opioid users, two weekly or monthly depot injections (CAM 2038, RBP-6000) and one implant (probuphine). The prospects of these new medications are significant by optimizing retention and compliance and minimizing the risk of diversion. Thus, these novel medications can facilitate treatment of OUDs significantly.

Citation: Soyka M, Franke AG. Recent advances in the treatment of opioid use disorders–focus on long-acting buprenorphine formulations. *World J Psychiatr* 2021; 11(9): 543-552

URL: https://www.wjgnet.com/2220-3206/full/v11/i9/543.htm

Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 24, 2021
Peer-review started: February 24, 2021
First decision: April 21, 2021
Revised: June 6, 2021
Accepted: August 4, 2021
Article in press: August 4, 2021
Published online: September 19, 2021

P-Reviewer: Sadee W
S-Editor: Fan JR
L-Editor: A
P-Editor: Wang LYT



DOI: https://dx.doi.org/10.5498/wjp.v11.i9.543

INTRODUCTION

Opioid use disorder (OUD) is defined as a chronic relapsing substance use disorder that causes psychological and physical harm. The economic burden and health costs of OUD are also very significant[1-4].

PREVALENCE

OUD has a prevalence of approximately 0.2%-0.4% in the adult population in many countries[5-7]. In Europe, heroin is the most frequently abused opioid. However, in other countries, the use of synthetic opioids and opioid pain killers, such as fentanyl or oxycodone, has been exploding and is the predominant form of opioid use. In particular, the United States is facing an epidemic of opioid pain killer abuse[8]. Recent data indicate that in Europe, there are 1.3 million high-risk opioid users and 644000 opioid users in substitution treatment[5]. Opioid use accounts for 40% of all drug requests in the European Union.

The high mortality in opioid dependence remains a significant problem. Opioids are involved in 82% of fatal drug-related overdoses[5]. Most opioid-related deaths are caused by overdose and respiratory depression. Other frequent causes of death include suicide, accidents, injuries, and numerous somatic disorders, such as infectious diseases (human immunodeficiency virus, hepatitis, others). In many fatal drug intoxications, polysubstance abuse is involved, especially alcohol or other sedative drugs[9].

TREATMENT AIMS

Opioid maintenance treatment (OMT) and psychosocial interventions are key elements in the treatment of OUD[2,8,10,11]. Major aims in the treatment of OUD are reduction of opioid use or even abstinence[12,13] as measured by self-reports or toxicological analysis, reduction of other substance use, improved social functioning and health outcome and reduction of criminal behavior[12,14,15].

There are numerous clinical and longitudinal studies on treatment outcomes in OUD. However, many long-term studies only address substance use or abstinence rates, whereas other outcome parameters are less often reported. An interesting study on outcome criteria has recently been described by Wiessing *et al*[16], who assessed reported outcome domains in 27 longitudinal studies (Table 1). Data indicate that many domains, especially social functioning or health economics, are often neglected as outcome parameters.

Several medications are currently available for the treatment of OUDs (Table 2). For approximately five decades, OMT has been the established and widely accepted first-line treatment of OUD[11,14,17-20]. In addition, a number of pharmacological options are available. Medications used in OMT control craving for opioids and withdrawal symptoms. The two widely examined gold standards in OMT are methadone and buprenorphine[21].

Oral methadone (standard doses 60-100/120 mg daily) and sublingual buprenorphine (standard doses 8-12, max 24-32 mg daily) are the primarily used drugs in the treatment of opioid dependence. Their efficacy has been shown in many clinical studies[17-19]. Some distinct pharmacological differences are noted between methadone and buprenorphine.

Methadone is a pure nonselective opioid receptor agonist of the mu, delta and kappa opioid receptors. Methadone induces the typical clinical effects of full opioid agonists, such as analgesia, sedation, respiratory depression, euphoria and tolerance. Methadone causes a significant physical dependence. Methadone has a half-life of approximately 22 h (13-50 h). Methadone blocks the opioid receptor for approximately 24 h, so it is suitable for daily dosing. Methadone suppresses opioid withdrawal symptoms for 24 h. There is broad evidence for the efficacy of methadone in OMT[14,17-19]. The drug is widely accepted and used.

Table 1 Large variations in outcome measures in longitudinal studies of opioid dependence[16]

Domain	Reported among 27 studies included
Drug use	21 of 27
Crime	13 of 27
Health	13 of 27
Treatment-related outcomes	16 of 27
Social functioning	13 of 27
Harms	8 of 27
Mortality	13 of 27
Economic estimates	2 of 27

Results are based on 27 studies included. Eight domains were defined. Each domain was reported x-times among 27 studies.

Table 2 Pharmacological options in the treatment of opioid use disorders

Drug	Onset of action, duration	Route of administration	Clinical use
Opioid antagonists			
Naloxone	Few minutes	i.v., nasal (spray)	Opioid overdose
Naltrexone	Daily	Oral	Abstinence
Naltrexone (depot)	One month	i.m.	Abstinence
Partial agonists			
Buprenorphine	Daily	Sublingual	Maintenance
Buvidal	Weekly, monthly	Subcutaneous	Maintenance
RB_6000 (sublocade)	Monthly	Subcutaneous	Maintenance
Probuphine	6 mo	Implant	Maintenance
Full agonists			
Methadone	Daily	Oral	Maintenance
Heroin	Hours	i.v.	Maintenance
Morphine sulfate (retarded)	Daily	Oral	Maintenance
Morphine sulfate	Daily	Oral	Maintenance

Buprenorphine, being a partial agonist at the mu-opioid receptor[11,19], has to be administered sublingually because of a strong first pass effect. Regarding opioid receptors, the use of buprenorphine is associated with a ceiling effect at these receptors. Compared to methadone, buprenorphine is at lower risk to induce depression of respiration. Numerous studies indicate that buprenorphine is associated with fewer fatal intoxications or overdose deaths than methadone. Other full opioid agonists used for the treatment of OUD include morphine sulfate and diacetylmorphine (heroin). Both are second line medications for OMT[11,14,22].

There are some significant problems in OMT. The most important factor is the risk of diversion of methadone or buprenorphine. Other major problems are concomitant opioid or other substance use as well as limited compliance and retention in treatment [20,23,24]. The latter is of great importance. A recent systematic review on retention in OMT[25] included four randomized clinical trials and 63 observational cohort studies with a total of 294592 patients. The overall findings indicate a 1-year retention rate of 57% and a 3-year retention rate of 38.4%. The retention rate is higher in patients with older age and depends on an adequate dose of the maintenance drug. Several studies indicate that a too low dosage is associated with a higher dropout rate[26].

Dosing issues are of great relevance in OMT. Adherence to treatment depends on adequate dosing, and retention can be improved by adequate dosing[13,27-29]. Too low doses of methadone or buprenorphine are associated with low retention and risk

of further substance use.

Methadone remains the most frequently used medication in OMT. The other first-line medication is buprenorphine[18,19,24,26,30,31]. The retention rate for buprenorphine was reported to be lower than that of methadone in some studies[19,26,30]. The risk for respiratory depression by buprenorphine in cases of overdose is lower than that for full opioid agonists[24,32].

Buprenorphine is used as a sublingual tablet. It is marketed as a monoproduct or in combination with naloxone (buprenorphine:naloxone ratio 4:1)[9,27]. Naloxone is a short-acting opioid antagonist and is pharmacologically active only as an i.v. medication and as a nasal spray for the prevention of overdose death. Naloxone will rapidly induce opioid withdrawal. The risk of precipitated opioid withdrawal should prevent the patient from injecting buprenorphine and thus reduce the risk of diversion or i.v. use of buprenorphine.

Both methadone and buprenorphine are administered as once a day doses, and both suppress symptoms of opioid withdrawal for 24 h. Longer dosing intervals have been a major aim in OMT research. A long-acting methadone analog was previously studied but had to be withdrawn over potential adverse cardiac effects[33,34].

Clinical and social reasons for long-acting opioids in OMT include a reduced risk of diversion, improved compliance, easier home dosing and longer treatment intervals. The recent coronavirus disease 2019 (COVID-19) epidemic has demonstrated that prolonged dosing and treatment intervals and consequently less time spent in the outpatient clinic or at the office-based physician, respectively, and reduced use of social and medical resources are important goals for many clinicians.

Recent developments

Exciting developments have occurred in recent years: Three different long-acting buprenorphine formulations have been developed, approved and in part introduced into clinical practice in many countries. These agents will be reviewed briefly.

RBP-6000 (Sublocade™)

RBP-6000 is a buprenorphine depot injection. It has been marketed in the United States since 2018 and will soon be available in Europe. Medication and dosing intervals: Monthly s.c. injections are available with dosages of 100 and 300 mg. Dosages recommended for the treatment of OUD (www.sublocade.com) include two initial 300 mg injections monthly followed by monthly 100 mg injections.

RBP-6000 has been studied in several pharmacological and clinical studies. Nasser *et al*[35] studied the effects of RBP-6000 in patients with opioid dependence. RBP was found to block the effects of a strong opioid, hydromorphone, such as opioid cravings. Other studies showed effective μ-opioid receptor blockade with different dosages of RBP-6000[35,36]. These findings suggest that RBP-6000 is a suitable medication for OMT. A recent combined analysis of phase II and III trials with 570 subjects[37] showed that therapeutic concentrations can be achieved from the first injection. These therapeutic concentrations were achieved during the entire treatment duration. The data suggest that the drug provided therapeutic plasma concentrations over the entire treatment duration.

Clinical data indicate that RBP-6000 is effective in OMT. Haight *et al*[38] performed a multicenter phase III study being double-blind and placebo-controlled. Dosing regimen among the opioid dependent patients was as follows: One group received monthly injections of RBP-6000 subcutaneously (6 × 300 mg or 2 × 300 mg) followed by 4 × 100 mg, the other group received placebo. Abstinence rates as a major outcome in both buprenorphine depot groups (n = 203 and n = 201 patients, respectively) were significantly higher than those in the placebo group (n = 100) (41.3% and 42.7% in the respective buprenorphine groups compared to 5.0% in the placebo group; P < 0.0001 for both buprenorphine groups). No differences in outcome were noted between the buprenorphine groups. Both studied dosing regimens were equally effective. In addition, the rate of hospital admissions was also lower in both buprenorphine groups compared with the placebo group[39]. Overall, these data indicate that RBP-6000 is effective. Andorn *et al*[40] performed an open-label multicenter study in 257 patients. A total of 13.2% of OUD patients had injection-site adverse events. Although these events are usually mild and transient, they may affect acceptance of this or other depot injections. Otherwise, the safety profile was good with fewer adverse events in the second 6 mo of treatment *vs* the first 6 mo. The retention rate was approximately 50% after 12 mo.

CAM 2038 (Buvidal®)

CAM 2038 is another novel depot buprenorphine injection. The drug is injected subcutaneously. Buvidal is approved in Europe[41,42]. Dosing regimen: Four different dosages are available: 8, 16, 24 or 32 mg for weekly injections and 64, 96, 128 or 160 mg for monthly injections. CAM 2038 treatment is typically initiated with weekly injections. Later, the patient can be transferred from weekly to monthly depot injections.

Several pharmacological studies have been conducted to explore the pharmacological effects of RBP-6000[43-45]. In sum, adequate plasma concentrations and bioavailability were demonstrated for the compound. Albayaty *et al*[45] showed that monthly or weekly subcutaneously administered depots of CAM 2038 (dosages: 96 mg and 192 mg) exhibited 5.7- to 7.7-fold increased bioavailability than sublingual buprenorphine (8, 16 or 24 mg). In addition, 24 mg and 32 mg Buvidal block the subjective effects of intramuscularly administered hydromorphone[44].

The efficacy of Buvidal has also been demonstrated in several clinical trials. In a phase III study being double-blind with double-dummy, with 428 patients[46], flexible weekly injections of CAM 2038 were used in the first 12 wk rather than monthly injections in the following 12 wk and tested against sublingual buprenorphine (flexible dose up to 24 mg daily maximum). Buvidal was found to be noninferior to sublingual buprenorphine with respect to opioid use (primary outcome) and opioid-free urine (secondary outcome). The average weekly CAM 2038 dosages were 24 mg, and monthly injections ranged over 100 mg. No novel adverse events were noted. The side effect profile of RBP-6000 is similar to that of sublingual buprenorphine[47]. With respect to the injection, mild local reactions were reported by 18%-22% of the participants. In a very recent study, injection site reactions of mild intensity were the most frequent adverse drug reaction[48]. Further safety data are being collected in an ongoing nonrandomized prospective observational study[49].

Buprenorphine implant (Probuphine™, Sixmo)

The third long-acting buprenorphine is an implant[1]. Probuphine was approved by the Food and Drug Administration (FDA) in 2016 for the long-term treatment of opioid dependent patients who were on a stable medication regimen of 8 mg buprenorphine sublingually or less. Buprenorphine (8 mg) is typically considered a moderate dose in OMT with an upper limit of daily sublingual buprenorphine dose of 24-32 mg. In Europe, the implant was approved by the European Medicine Agency in 2019. Buprenorphine is linked to a polymer that delivers the drug steadily to the body. Four implants are inserted. The dose of the buprenorphine released by the implant is equivalent to 8 mg sublingual buprenorphine or less[50-52]. Subdermal insertion of the implant requires minimal surgery. The implant is inserted in the upper arm and remains there for 6 mo before it is removed again. Plasma concentrations peak 12 h after the implant is inserted. Steady state conditions were noted after 3-4 wk[52].

Several relevant clinical studies of Probuphine are available. The efficacy of the buprenorphine implant was demonstrated in three double-blind studies (309 patients included) with a follow-up of up to 6 mo.

In a randomized controlled trial Ling *et al*[53] assessed 163 participants with opioid dependence over a period of 6 mo. After initial treatment with sublingual buprenorphine, the patients were transferred to either 4 × 80 mg buprenorphine or placebo implants. The retention rate in the implant group (71 of 108 patients) was significantly higher than that in the placebo group (17 of 55 patients; 65.7% *vs* 30.9%, $P < 0.001$). In the buprenorphine implant group, the number of opioid-free urine samples was higher.

Rosenthal *et al*[54] conducted a placebo-controlled randomized clinical trial in opioid-dependent patients who either received 4 × 80 mg buprenorphine ($n = 114$) or 4 placebo implants ($n = 54$). In an open design, the control group was treated with sublingual buprenorphine at a dose of 12-16 mg daily. In total, 119 participants were included in the control group. Compared to the placebo group, the retention rate of the implant group was significantly higher ($P < 0.0001$) (64 *vs* 26%). Furthermore, regarding the mean number of urine samples being opioid-free, the implant group was also found to be superior to the placebo group and noninferior to the sublingual buprenorphine group. Side effects: Negligible (local) reactions among the patients of the implant group were more or less frequent (25%-27%).

Furthermore, Rosenthal *et al*[55] studied OMT patients being stably adjusted to a sublingual dose of 8 mg (or less). Patients were given sublingual placebo plus four buprenorphine implants or sublingual buprenorphine plus four placebo implants over a period of 24 wk. In total, 177 patients were included. Over a time period of 6 mo, the

rate of abstinence among patients in the buprenorphine implant group was found to be noninferior to that in the control group treated with sublingual buprenorphine (85.7% *vs* 71.9%). The retention rate was 93%. The response rate was 96.4% in the buprenorphine implant group and 87.6% in the control group ($P < 0.01$). In addition, 85% of patient in the implant group were opioid free compared to 72% of the patients of the control group.

According to the FDA there is the necessity of a special risk management for this treatment. The "Probuphine Risk Evaluation and Mitigation Strategy" program was initiated (https://probuphinerems.com).

In addition, Titan Pharmaceuticals announced discontinuing United States Probuphine implant sales on October 15, 2020. No specific medical reasons were given for this decision.

DISCUSSION

OMT is the established first-line treatment in OUD, and methadone and buprenorphine serve as the pharmacological "frontrunners"[21]. Buprenorphine has a good safety profile[56] but modest and somehow lower retention rates than methadone. Retention to treatment is of overwhelming importance for treatment outcome and mortality in OUD, especially the induction phase and the period after leaving treatment[15]. Other common problems include diversion and i.v. use of buprenorphine[3,57]. Whether the combination of buprenorphine and naloxone lowers the risk of buprenorphine diversion is controversial[58].

Emerging or approved long-acting buprenorphine (depot or implant) formulations significantly widen the therapeutic arena in OMT[42,59]. Weekly and monthly s.c. buprenorphine injections as well as 6-mo depot formulations are available or will be available in the near future. It is clear and self-evident that the retention to treatment in patients with a depot formulation will be greater than that noted in patients in conventional OMT, and the risk of diversion is especially minimal to nonexistent. The data reviewed indicate that long-acting buprenorphine formulations are as efficient as sublingual buprenorphine with respect to opioid use with a similar side effect profile–with the exception of effects linked to injection or insertion of the compound. To date, some other observational studies on these medications are ongoing to provide further safety data[49,60].

The clinical question is: Who will benefit?

With the long-term French buprenorphine experience in mind, Vorspan *et al*[61] suggest prolonged-release buprenorphine depot formulations, such as Buvidal, as a promising treatment option in the following scenarios: (1) OMT initiation, including in nonspecialized medicine care; (2) Discharge from prison or hospital; (3) Diversion /Misuse of buprenorphine or methadone; and (4) Clinically stabilized patients wishing to avoid daily oral taking of the medication.

In addition, clinically stabilized patients wishing to receive an injection or implantation of the compound can be transferred to a buprenorphine depot.

This covers a wide range of patients. Other authors have similar views. Ling *et al*[39] stated that "Anyone with an OUD who can benefit from oral buprenorphine can benefit from the injectable".

Patients who want to avoid daily oral intake of the medication may be attracted by the prospect of more personal freedom.

In addition to benefits at the individual level, this novel medication also provides public health benefits. Retention rates may be increased–which has to be shown in future studies–and the risk for diversion may be reduced. In addition, the utilization of health care resources will be reduced. These effects are relevant, especially during the COVID-19 pandemic when social distancing is required[42].

Arunogiri and Lintzeris[62] argued that the use of long-acting buprenorphine formulations may help during the COVID-19 pandemic, and some health care organizations have advocated its use[42]. For example, a rapid upscaling of Buvidal use in custodial settings occurred in Australia during the COVID-19 epidemic[63].

Depot formulations are already used in prisons or forensic psychiatry settings to avoid diversion of the drug[61]. Broad empirical evidence suggests that OMT can reduce criminality in OUD[64-68] as reported in a meta-analysis by Moore *et al*[69]. The risk of diversion and misuse of opioid medication is significant in prison settings. Depot medications may reduce this risk significantly.

There are also some practical aspects to be considered. Although transfer from sublingual to depot buprenorphine will likely not represent a major problem, the introduction of depot buprenorphine to a patient previously treated with methadone is more complicated. Moreover, there are few studies on this issue. Switching the patient from methadone to sublingual buprenorphine first before transferring him to a depot formulation seems to be the most appropriate method at present.

Patient preferences and attitudes toward treatment are of great relevance for OMT. Many patients prefer certain OMT medications.

There are very few qualitative studies on this issue[70-73]. Patients cite spending less time with drug-treatment services, having more time for other activities and avoiding the stigma of being in OMT as reasons for preferring depot medications[39].

CONCLUSION

In conclusion, novel depot buprenorphine formations are a promising therapeutic option in OMT. There is no doubt about the efficacy of these compounds, but the practical value has to be shown in real life conditions.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 September 19; 11(9): 553-567

DOI: 10.5498/wjp.v11.i9.553

ISSN 2220-3206 (online)

MINIREVIEWS

Is there a place for cellular therapy in depression?

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Author contributions: do Prado-Lima PAS was responsible for the overall organization of the manuscript structure and writing and reviewing the epidemiological part of depression and the inflammatory role in this psychiatric disorder for the survey and comments related to clinical trials involving stem cell depression that are in progress; Costa-Ferro ZSM and Souza BSDF were responsible for compiling, organizing, and description of the tables related to the main studies involving stem cells in depression and other associated diseases; da Cruz IBM was also responsible for reviewing the neuroinflammatory aspects related to depression, the general organization of the figure, formatting, and submission of the manuscript; all authors contributed to the general writing, revising the text, and scientific quality of the manuscript.

Supported by Conselho Nacional de Desenvolvimento Cientifico - CNPq.

Conflict-of-interest statement: The

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Abstract

Although efforts have been made to improve the pharmacological treatment of depression, approximately one-third of patients with depression do not respond to conventional therapy using antidepressants. Other potential non-pharmacological therapies have been studied in the last years, including the use of mesenchymal stem cell therapies to treat depression. These therapies are reviewed here since it is clinically relevant to develop innovative therapeutics to treat psychiatric patients. Experimental data corroborate that mesenchymal stem cell therapy could be considered a potential treatment for depression based on its anti-inflammatory and neurotrophic properties. However, some clinical trials involving treatment of depression with stem cells are in progress, but with no published results. These studies and other future clinical investigations will be crucial to define how much mesenchymal stem cells can effectively be used in psychiatric clinics as a strategy for supporting depression treatment.

Key Words: Mood disorders; Stem cells transplant; Mesenchymal stem-cells transplant; Inflammation; Immunomodulation; Depression

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authors declare that they have no conflict of interest.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 28, 2021
Peer-review started: February 28, 2021
First decision: April 20, 2021
Revised: May 5, 2021
Accepted: August 13, 2021
Article in press: August 13, 2021
Published online: September 19, 2021

P-Reviewer: Byeon H, Sun C
S-Editor: Wang JL
L-Editor: A
P-Editor: Wang LYT

Core Tip: In this study, the authors performed a narrative review regarding the role of inflammation in depression and investigated the evidence suggesting that the use of stem cell therapies could be a realistic, safe, and effective strategy for treating depression.

Citation: do Prado-Lima PAS, Costa-Ferro ZSM, Souza BSF, da Cruz IBM, Lab B. Is there a place for cellular therapy in depression? *World J Psychiatr* 2021; 11(9): 553-567
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/553.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.553

INTRODUCTION

Depression is a highly prevalent disorder that affects the entire life span. In adults, the 12-mo prevalence of the major depressive disorder is approximately 6%[1], and the lifetime risk is 15%-18%[2]. It is one of the leading causes of disability worldwide[3]. In clinical terms, depression is a complex disorder with devastating consequences for patients and their families, provoking psychological suffering due to sadness, anxiety, anguish, and guilt; diminished cognitive performance; and impaired attention, memory, and reasoning. Moreover, depression has negative influences on decision-making and interpretation of facts, leading to wrong decisions. Depression is also a risk factor for the development and outcome of many chronic non-transmissible diseases, such as cardiovascular diseases and diabetes[4-6]. Evidence also suggests a small and positive association between depression and the overall risk of cancer, including liver and lung cancer[7].

Pharmacological treatment for depression has been available since 1957, when imipramine, a tricyclic antidepressant, and iproniazid, a monoamine oxidase inhibitor, were released[8,9]. In more than six decades, many drugs have been released commercially, improving the tolerability and safety of antidepressant treatment. However, with few exceptions, these medications' intended mechanism was to increase serotonin, noradrenaline, and dopamine availability. Although efforts have been made to improve pharmacological treatment of depression, approximately one-third of patients fail to respond to conventional antidepressants[10]. This limitation in the antidepressive efficiency is possibly related to the mechanism of action of the available antidepressants. Therefore, it is clinically relevant to develop innovative therapeutic strategies based on the pathophysiological aspects of depression.

Several lines of evidence suggest that chronic inflammatory states may be related to depression etiopathogenesis in recent years. This evidence made way for researchers to develop new anti-inflammatory therapies that could alleviate symptoms and the progression of depression[11,12]. In a previous study, our group investigated the possible use of stem cell therapy. Our hypothesis was based on the anti-inflammatory and neurodegenerative properties of stem cells, which could treat the pathogenic state that maintains depression.

Here, we performed a narrative review regarding the role of inflammation in depression and investigated the evidence suggesting that the use of stem cell therapies could be a realistic, safe, and effective strategy for treating depression.

INFLAMMATION PROVOKING DEPRESSION

A colossal research effort has been made in the last 60 years to unravel and understand the neurobiological processes underlying depression. This process started since tricyclic and monoamine-oxidase effectiveness in depression treatment was proven in 1957[13], and pharmacological drugs have been introduced in clinical practice. The attempt to identify the neurobiological processes and causes of depression started with understanding the antidepressant mechanisms of action. This strategy led to the identification of monoamines and their role in depression. Further, the development of almost all antidepressant medications was based on these discoveries.

In 1968, Carrol *et al*[14] postulated the role of the hypothalamus-hypophysis-adrenal axis (HPA axis) in depression etiopathogenesis, subsidizing the HPA axis hypothesis. The role of glucocorticoid hippocampal receptors in HPA-axis modulation in

depression has been extensively studied. Chronic stress modulates the inflammatory process that plays a crucial role in the neurobiological aspects underlying depression [15]. However, this research strategy has not led to the development of antidepressant medications.

The interest in the role of immunological and inflammatory mechanisms in depression is a natural consequence of HPA axis studies since cortisol can modulate these responses. Furthermore, consistent data on the role of psychological stress on depression development involves alterations in immune functions, mainly due to chronic inflammatory states[16,17].

The link between emotional stress, depression, and inflammation seems to involve evolutionary issues. Several lines of evidence suggest that metabolic, endocrine, and immune responses co-evolved, helping animal surveillance since animals need to actively seek food by exposing themselves to injury or predation and also need to defend themselves from pathogens[18].

In addition to triggering a fight or flight response, stress is characterized by increases in heart rate, blood pressure, cortisol, and catecholamines. It also activates inflammatory pathways in peripheral blood mononuclear cells[9]. However, when stress exposure occurs continuously without being resolved, metabolic and physiological responses are triggered that contribute to the formation of chronic inflammatory states[19]. Figure 1 shows the association between stress and neuroinflammation in depression etiopathogenesis based on several previous reviews[14,18,20].

HOW CHRONIC STRESS, THROUGH INFLAMMATION, CAN TRIGGER DEPRESSION?

Although acute stress induces an immunosuppressed state, chronic stress exposure has an antagonistic pro-inflammatory effect. As a result, the anti-inflammatory state develops to a chronic inflammatory condition due to the factors produced by exposure to chronic stress, such as catecholamines[19].

Catecholamines released by psychological stress can promote damage-associated molecular patterns (DAMPs), including high mobility group box 1 (HMGB1), ATP, and heat shock proteins. DAMPs are inflammatory signaling proteins released by different stress levels, including psychological factors[21,22]. For example, HMGB1 is a nuclear protein that is present in all cell types.

Once released, it activates through TLR4 and RAGE receptor inflammatory cascades, including the pyrin domain-containing protein 3 (NLRP3) inflammasome[20,23]. Inflammasomes are cytosolic protein complexes formed in myeloid cells, such as monocytes, in response to pathogenic microorganisms or sterile stressors, such as psychological stress. Activation of the NLRP3 inflammasome subsequently leads to caspase-1 activation, which in turn provokes cleavage of the pro-inflammatory cytokines interleukine-1β (IL-1β) and IL-18[20], and nuclear factor-κB (NF-κB) pathway activation with subsequent IL-6 release[21].

All events occurring outside the brain must change the brain physiology to trigger depression. There are three mechanisms by which inflammation in peripheral tissues reaches the brain, overcoming the blood-brain barrier (BBB). In the humoral pathway, pro-inflammatory cytokines, such as IL-1β, IL-18, IL-6, and TNFa, enter the brain through the leaky region of the BBB, such as circumventricular organs, or the binding of these cytokines to saturable transport molecules in the BBB[9]. In the neural pathway, the same cytokines bind peripheral afferent nerve fibers, such as the vagus nerve, which stimulates catecholaminergic fibers in the brain and translates into central cytokine signals. Moreover, activated immune cells, such as monocytes, reach the brain vasculature and parenchyma through trafficking mechanisms[9]. These different mechanisms act in coordination to trigger inflammation in the brain. For example, peripheral TNFa can stimulate microglia to produce CC-chemokine ligand 2 (CCL2), a chemokine that attracts monocytes to the brain[24]. Cytokines such as IL-1β and TNFa can also stimulate astrocytes to produce chemokines such as CCL2 or CXC chemokine ligand 1, thus attracting immune cells to the brain[25].

Peripheral inflammatory molecules induce astrocytes and microglia activation into the brain, triggering a complex inflammatory cascade. This cascade interferes with neurotransmission, the HPA axis, and neurotrophin balance synapses. An example of the peripheral effects on neuroinflammation is the expression of IL-1β and TNFa. These cytokines can induce the overexpression of some molecules, such as p38 mitogen-activated protein kinase, which alters the serotonin transporter, leading to a

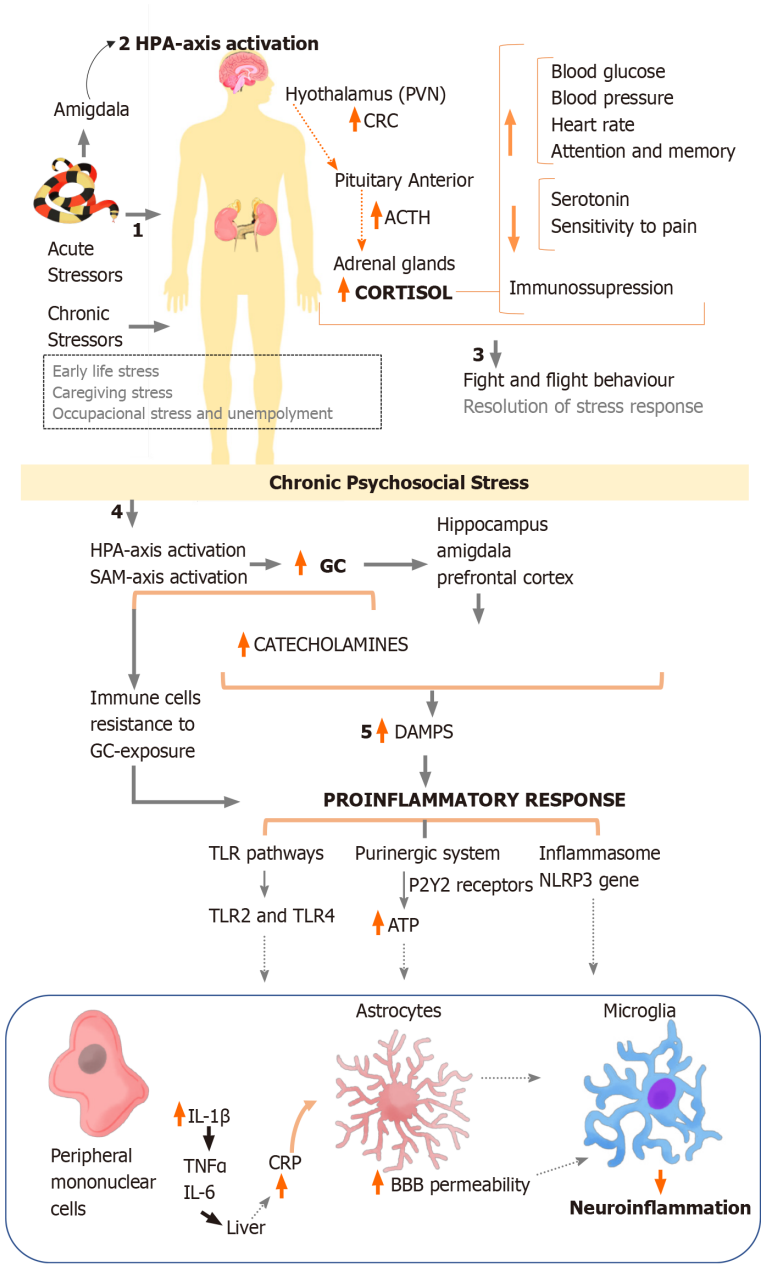


Figure 1 Synthesis of stress acute and chronic response on the inflammatory pathway. (1-2) Stressors trigger a primary neuroendocrine response from the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamic Parvocellular neurons from the paraventricular nucleus secrete a corticotrophin-releasing hormone (CRH) and vasopressin. CRC induces, subsequently, the anterior hypophysis to release the adrenocorticotropic hormone, leading to a glucocorticoid secretion (cortisol in humans and corticosterone in rodents) by the adrenal cortex; (3) Acute physiological alterations prepare the human to fight or flight from stressors. These are evolutionary adaptive behaviors related to surveillance. Therefore, stress induces transient activation of HPA- axis activity paralleled by temporary increases in CRH transcription. Sympathetic-Adreno-Medullar axis is also activated in the stress response causing several physiological systemic changes. Acute stress also leads to an immunosuppressive state; (4) On the contrary, the exposure to chronic stress leads to excessive sustained elevated levels of stress hormones, including CRH and corticosterone, can be harmful and predispose to risk of several chronic non-transmissible diseases, including psychiatric disturbs; (5) And mechanisms involving an increase in neural apoptosis an in the levels of some molecules associated to stress response, especially catecholamines. These processes induce the production of immunogenic Damage-associated molecular patterns (DAMPs) molecules. (6) DAMPs can activate at least three inflammatory pathways that contribute to the increase of brain-blood barrier permeability, promoting ingress of some systemic peripheral inflammatory cells into the brain contributing to the neuroinflammatory states cause dysfunction and increase the risk of depression. HPA: Hypothalamic-pituitary-adrenal; PVN: Paraventricular nucleus; CRH: Corticotrophin-releasing hormone; VP: Vasopressin; ACTH: Adrenocorticotropic hormone; GC: Glucocorticoid; SAM: Sympathetic-Adreno-Medullar; DAMPs: Damage-associated molecular patterns; BBB: Brain-blood barrier.

decrease in the availability of serotonin in the synaptic cleft[9].

IL-6, another pro-inflammatory cytokine, contributes to the generation of high levels of reactive oxygen and nitrogen species, which cause oxidative stress. This reaction decreases tetrahydrobiopterin (BH4) availability, a cofactor enzyme in monoamine synthesis, diminishing serotonin, noradrenaline, and dopamine availability. The cytokines, particularly IL-1β and TNFa molecules, alter the kynurenine pathway by

increasing quinolinic acid levels (QA). The elevation of QA levels occurs by the activity of the indoleamine 2,3-dioxygenase enzyme, which catalyzes tryptophan into kynurenine. As QA synthesis involves tryptophan, depletion of this amino acid directly affects serotonin production. Furthermore, QA has a dangerous effect on the brain by increasing oxidative stress, astrocyte degeneration, and neuronal apoptosis. Therefore, inflammatory activation generates metabolic alterations that can contribute to the risk of depression and suicide[9,16,26-28].

QA and cytokines also have a critical synergistic effect on glutamate metabolism. QA directly stimulates N-methyl-D-aspartate receptors (NMDA), decreasing glutamate re-uptake and stimulating glutamate release by astrocytes[9]. In astrocytes, pro-inflammatory cytokines decrease the expression of glutamate re-uptake pumps, increasing glutamate release. This combined action triggers high glutamate levels inside and outside the synapses, allowing the activation of extra-synaptic NMDA receptors. Alterations in the glutamatergic pathway induce a decrease in molecules with neurogenic functions, particularly brain-derived neurotrophic factor (BDNF)[9,29,30]. It should be noted that conventional antidepressant medication acts by increasing monoamine availability in the synapse, thereby increasing BDNF and consequently promoting neurogenesis through BDNF action on its receptor TrkB[31,32].

The effect of neuroinflammation has an impact on neurocircuit function. Inflammation has been associated with a decrease in responsiveness to reward stimuli, particularly in the ventral striatum. For example, in healthy volunteers, the administration of low doses of endotoxin, which can increase pro-inflammatory cytokine levels more safely, is associated with the development of depressive mood. This effect was related to the diminished activity of the ventral striatum to the anticipated reward measured by functional magnetic resonance imaging (fMRI)[33]. Interferon-a administration to treat chronic hepatitis virus C infection-induced depression, anhedonia, and fatigue. This administration reduced ventral striatum activation with reward-anticipatory stimuli during fMRI. In the same study, positron emission tomography demonstrated an association between the behavior and fMRI results with 18F-dopa turnover in the ventral striatum; changing presynaptic dopamine function was consistent with decreased dopamine synthesis or release[34]. Evidence also described that typhoid immunization could produce inflammation by IL-6 augmentation and activation of the subgenual anterior cingulate cortex (sgACC), a region implicated in depression and depressive symptoms. Moreover, the elevation in IL-6 concentrations decreases the connectivity between the sgACC and amygdala, medial prefrontal cortex, superior temporal sulcus, and ventral striatum[35].

Many of these brain changes induced by peripheral inflammation and neuroinflammation have been described in experimental and epidemiological studies that involve chronic exposure to social stress. Exposure to social stress can increase soluble TNFa receptors and IL-6 molecules. The elevation of soluble TNFa receptor can increase the dorsal ACC and anterior insula activity, two brain regions that process rejection-related distress and negative affect[36,37]. Experimental protocols where stress was induced in the laboratory conditions described the increased feelings of social and rejection behaviors associated with inflammatory activation by increasing IL-6 Levels and high left amygdala activity, a brain area directly related to detection and response threats[38].

Child abuse is one of the main risk factors for chronic stress and inflammation in the etiopathogenesis of depression. Early adversity is considered a risk factor for developing depression, and emotional abuse shows the strongest association, followed by neglect[39]. A growing body of literature showed that early adversity could shape immune cells and inflammatory cascades. A meta-analysis performed by Baumeister *et al*[40] showed that adult individuals exposed to childhood trauma had elevated baseline blood levels of C-reactive protein, IL-6, and TNFa.

Therefore, the pieces of evidence commented here can support the hypothesis that depression is an inflammatory disease. A meta-analysis showed higher peripheral levels of IL-6, TNFa, IL-10, IL-12, IL-13, IL-18, CCL2, IL-1b receptor antagonist, soluble IL-2 receptor, and soluble TNF receptor 2 in depressive patients. In comparison, the INFγ blood levels were lower in these individuals. Moreover, the concentrations of IL-1b, IL-2, IL-4, IL-8, IL-5, CCL3, IL-17, the soluble IL-6 receptor, and the transforming growth factor-beta one did not present differences associated with depression[41].

ANTIDEPRESSANTS AND ANTI-INFLAMMATORY DRUGS ON DEPRESSION

As inflammation could trigger depression, the logical question is that anti-inflammatory drugs could positively affect depression. A recent meta-analysis on this issue included studies involving the impact of anti-depressive drugs on different pro and anti-inflammatory cytokines (IL-1b, IL-2, IL-4, IL5, IL-6, IL-8, IL-10, IL-12, TNFa, INFy, and others)[42]. Moreover, the meta-analysis found that antidepressant responders had lower levels of IL-8 than non-responders. Antidepressant treatment only decreased TNFa levels, IL-5, and granulocyte-macrophage colony-stimulating factor in responsive patients. However, when treatment-resistant patients were compared to non-depressed controls, IL-6, IL-8, TNFa, C-reactive protein (CRP), and macrophage inflammatory protein-1 were associated with poor treatment outcomes[43].

Furthermore, it has been tested for its potential anti-inflammatory use in the attenuation of depressive symptoms. A meta-analysis of randomized controlled trials showed an antidepressant effect of anti-cytokine drugs[44]. The anti-TNFa adalimumab and etanercept, except infliximab, showed an antidepressant effect. Previous studies have also described some antidepressant effects of dupilumab, an antagonist drug of the alpha subunit of the IL-4 receptor, and ustekinumab, which inactivates IL-12 and IL-23 cytokines[45]. Randomized controlled clinical trials have described the anti-depressive effect of some anti-inflammatory drugs such as (1) Glycyrrhizic acid, an HMGB1 inhibitor, was useful as an add-on with selective serotonin re-uptake inhibitor in the treatment[45]; (2) Minocycline, a tetracycline antibiotic, that lowers neuroinflammation by inhibiting microglial activation and inhibiting the release of HMGB1[46]. However, minocycline was effective only in patients with baseline levels of CRP > 2.8 mg/L[47]; and (3) Although bipolar disorder (BD) is not in the scope of this review, a clinical trial stands out here describing that coadministration of N-acetylcysteine and aspirin for 16 wk was associated with a reduction in depressive symptoms in BD-patients[48].

Despite the evidence suggesting that anti-inflammatory drugs could help treat depression, further investigations are needed to evaluate the safety of prolonged periods of anti-inflammatory co-treatments in patients with depression[49]. In this context, the search for non-pharmacological anti-inflammatory therapeutic strategies is of great interest to the psychiatric clinic, as in the case of stem cell treatments, which have been applied in other clinical areas, has been intensively investigated for more than 10 years[50,51].

CLINICAL USE OF ADULT STEM CELLS

Stem cells are defined as adult unspecialized cells with self-renewal ability and high regenerative potential[52,53]. Adult stem cells can differentiate into several cell lines and activate or inhibit a sequence of molecules involved in anti-inflammatory and anti-apoptotic pathways[52,53]. Mesenchymal stem cells (MSCs) were first detected in the bone marrow. However, they can also be isolated from the umbilical cord tissue and adipose tissue, among other sources[52-57].

Stem cells were first described in the middle of the 20th century in mouse models [58,59], and stem cell transplantation was first applied in humans in 1957[60,61]. In the following decades, bone marrow stem cells-transplants have saved the lives of patients suffering from a great variety of diseases, mainly conditions affecting the hematopoietic or immunological system. Due to relatively low MSC-immunogenicity, the transplantation of these cells presents a low risk of tumorigenicity and less complicated ethical/regulatory issues compared to embryonic pluripotent stem cells [57,62].

Studies of therapeutic MSCs applications have expanded, showing that both allogeneic and autologous transplantation is possible due to the low immunogenicity of these cells and immunomodulatory effects[63]. These studies, including experimental investigations performed in several animal models of inflammatory and autoimmune-mediated disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and myasthenia gravis[64-66] and other conditions associated with inflammatory disturbances such as sepsis[67], lung fibrosis[68], diabetes[69], atherosclerosis [70], and osteoarthritis[71].

STEM CELLS-BASED THERAPIES FOR NEUROINFLAMMATORY DISORDERS

Stem cell therapies have emerged as a standard for the treatment of both subacute and chronic inflammatory processes and neurological disorders. Investigations have suggested the potential use of adult stem cells therapy to treat several neurological conditions, such as multiple sclerosis[72], autoimmune encephalomyelitis[73], Alzheimer's disease, and other dementia conditions[74], Parkinson's disease[75], and epilepsy[76]. Most studies emphasize the immunomodulatory nature of adult stem cells, with its therapeutic efficiency related to neurological diseases, particularly triggering anti-inflammatory states.

For example, in epilepsy, seizure activity can induce pro-inflammatory molecules, therefore affecting the severity and frequency of seizures[77]. Transplantation of bone marrow mononuclear cells (BMMCs) or human umbilical cord blood mononuclear cells in experimental epilepsy models induced significant improvements in neurological function[78,79]. After a seizure, brain injury induces a highly regulated cascade of biological events, characterized by the release of cytokines, chemokines, and protectins in the neuronal microenvironment[80,81], which was attenuated by adult stem cell transplantation, decreased the inflammatory states, and promoted tissue repair through cell-cell interactions and paracrine effects[80-83]. Furthermore, some evidence showed that adult stem cells stimulate angiogenesis and endothelial repair through paracrine actions[82,83]. In Alzheimer's disease, MSCs have been shown to reduce IL-1, IL-2, TNFa, and IFN-γ in the serum and oxidative stress, which showed an anti-inflammatory effect[84].

Among the most relevant stem cells' action mechanisms is the release of extracellular vesicles carrying soluble factors, microRNAs, and organelles[85]. Initially, the release of extracellular vesicles was thought to represent a disposal mechanism by which cells eliminate unwanted proteins and other molecules. Among the extracellular vesicle subtypes, significant attention has been given to exosomes. Exosomes are small membrane vesicles with a diameter between 40 and 100 nm[86], and different biological molecules, including proteins, lipids, and nucleic acids that may be captured and act in a biologically active manner on recipient cells. Various studies have described the beneficial actions of MSCs by delivering exosomes instead of cells[87, 88]. Therefore, MSC cells or exosome transplantation could offer an efficient and safe non-pharmacological therapy to treat neurological conditions.

POTENTIAL USE OF BMMCS AND MSCS IN DEPRESSION: EVIDENCE FROM PRECLINICAL STUDIES IN EXPERIMENTAL MODELS

The optimistic results obtained from experimental studies involving BMMCs and MSCs in the therapy of neurological conditions open the perspective of developing non-pharmacological cell treatments for psychiatric disorders. The main results of these studies are presented in Table 1. The potential therapeutic effects of adult cells-based therapies have been well characterized across *in vivo* studies of depression models, including an investigation performed by our research team[89]. This study evaluated the effect of BMMCs transplantation on the restoration of sucrose preference in rats subjected to chronic stress. This well-established model triggers depressive symptoms in animals. The study also evaluated the potential inflammatory modulation of BMMCs in stressed rats. The levels of pro-and anti-inflammatory cytokines in different brain areas, blood, and spleen were also quantified. In this protocol, escitalopram was used as a positive antidepressant control. The results demonstrated that BMMCs transplantation in stressed rats: (1) Restored spontaneous sucrose consumption in stressed rats; (2) Had a robust anti-inflammatory effect, increasing the levels of the anti-inflammatory cytokine IL-10 in the amygdala, hippocampus, frontal cortex, other brain areas, and in the spleen and blood; a lowering effect on pro-inflammatory cytokine levels (IL-1 β, IL-6, TNFa, and INF-γ) was also detected in the same brain and peripheral tissues; and (3) Decreased levels of oxidized DNA quantified by 8'2-deoxyguanosine. In summary, the therapeutic use of BMMCs presented a positive impact on symptoms of depressed rats, and possible mechanisms involved in this effect include immunomodulation of inflammatory states in both the peripheral and central nervous systems.

Another recent study performed by Huang *et al*[90] team verified the results involving potential therapeutic MSC-transplantation in depression by anti-inflam-

Table 1 Concise information of some studies on the effects of administration of mesenchymal stem cells with different sources and exosomes

Ref.	Type and characteristics of animal model used	Timing of intervention with cells after insult	Type of cells infused and route of administration	Major finding
do Prado-Lima *et al*[89], 2019	Wistar rats; depression, induced with CMS	30th day of the CMS protocol	BMMCs from mice. Single-dose (1 × 10^{7} cells). i.v.	Anti-inflammatory effects; Reduction of pro-inflammatory cytokines; increased expression of anti-inflammatory cytokines; BMMCs decreased 8'2-deoxyguanosine level
Huang *et al*[90], 2020	C57BL/6 mice; depression-induced with CMS	21th day of the CMS protocol	ADSCs from C57BL/6 mice; Repeated i.v. (3 times) 1 × 10^{6} cells/dose	ADSC treatment improved depressive-like behaviors. Reduced the expression of inflammatory factors in the serum Reduced microglial activation in the hippocampus
Kin *et al* [91], 2020	Wistar Kyoto rats model of treatment-resistant depression	Day zero	MSCs from the bone marrow of Wistar rats. Single-dose 3 × 10^{5} cells/5 µl i.v.	MSCs encapsulation enhanced the treatment effects of MSCs in an animal model of treatment-resistant depression
Li *et al* [92], 2020	Mice model depression induced by CUMS	14th to the 42nd day CUMS protocol	MSCs lines from human umbilical cords (hUC-MSCs); Repeated (4 times) 1 × 10^{6}/ dose i.v.	The hUC-MSCs treatment improved the anxiety-like behaviors of CUMS, decreased pro-inflammatory factor levels, and increased anti-inflammatory factor levels. The hUC-MSCs inhibit microglial M1 polarization and the level of inflammation factors. The hUC-MSCs can alter the polarization of microglia by inhibiting C3a-C3aR signaling from reducing neuroinflammation. The hUC-MSCsdecreased neuronal damage and synaptic deficits
Guo *et al* [93], 2020	Sprague Dawley rats; Depression model by corticosterone injection	Day zero	BMSCs-derived exosomes 1 mL exosomes (100 µg/ 1 mL PBS) i.v.	BMSCs-derived exosomes improved hippocampal neuron injury of rats with depression by upregulating miR-26a
Li *et al* [94], 2020	Male BALB/c mice depression, induced by CS	After 30 days of the CMS protocol	Exosomes from NK cells one time. Exosomes 66.42 µg i.v.	The exosomes miRNA-containing from NK cells could alleviate symptoms of chronic mild stress in mice. miRNA decreased the levels of pro-inflammatory cytokines (I L-1β, IL-6, and TNFα) released by astrocytes in vivo; Exosomes with low miR-207 levels showed decreased antidepressant activity in vivo experiments. Exosomes with low miR-207 levels showed decreased antidepressant activity MiR-207 could reduce the release of pro-inflammatory cytokines in vitro

BMMCs: Bone marrow mononuclear cells; ADSCs: Adipose-derived mesenchymal stem cells; CMS: Chronic mild stress; CS: Chronic stress; BDNF: Brain-derived neurotrophic factor; TrkB: Tyrosine receptor kinase B; BV2: Microglial cells; eMSC: Capsules with MSCs; hUC-MSCs: Human umbilical cord mesenchymal stem cells; CUMS: Chronic unpredictable mild stress model; miR-26a: MicroRNA-26a; SOD: Superoxide dismutase; MDA: Malondialdehyde; LDH: Lactate dehydrogenase; TNFα: Tumor necrosis factor α; IL-1β: Interleukin-1β; NK: Natural killer cells; i.v.: Intravenously injected.

matory action. The experimental protocol used adipose-derived mesenchymal stem cells (ADSCs) injected into C57BL/6 mice on the 21st day of a protocol of 42 d of chronic mild stress (CMS). The animals were tested by three behavioral assays: sucrose preference, tail suspension, and forced swimming test. All tests are broadly recognized as behavioral assays to identify depressive and anti-depressive chemical and behavioral factors. ADSC transplantation remedied depressive-like behaviors. The authors also observed that ADSC treatment reversed and prevented the increase in the production of some pro-inflammatory cytokines (CCL2, TNFa, IL-1β, and IL-6) in the serum and promoted the expression of BDNF and its receptor TrkB in the brain tissue. ADSC treatment increased the nuclear factor-E2 related factor 2 (Nrf2), which in turn has an anti-inflammatory effect by inhibiting TLR4/NF-κB pathway activation. Immunofluorescence detection revealed that the number of ionized calcium-binding adaptor molecule 1 (Iba1+), a protein expressed only in microglia and involved in its activation, decreased after ADSC treatment. In the same study, Nrf2-modified ADSCs were co-cultured with microglia cells and then exposed to lipopolysaccharide (LPS). Nrf2 downregulation decreased the protective effects of ADSCs against LPS-induced microglial activation and M1 polarization; however, Nrf2 overexpression markedly suppressed LPS-induced TLR4/NF-κB expression in microglial cells[90].

Kin *et al*[91] implanted the encapsulated MSCs (eMSCs) into the lateral ventricle and observed antidepressant effects *via* neurogenic pathways in Wistar Kyoto rats. These rats exhibited congenitally higher depression-like behaviors and resistance to conventional antidepressant treatments. Therefore, Kyoto rats are considered a promising model for treatment-resistant depression. The implantation of eMSCs counteracted

depressive-like behavior on days 13 to 15 after implantation and enhanced endogenous neurogenesis in the subventricular zone and the dentate gyrus of the hippocampus. The eMSCs displayed a robust and stable secretion of vascular endothelial growth factor, BDNF, fibroblast growth factor 2, and ciliary neurotrophic factor. Implantation of eMSCs into the lateral ventricle activated relevant pathways associated with these growth factors.

Li *et al*[92] described the therapeutic action of human umbilical cord MSCs (hUC-MSCs) on chronic middle stress in mice. The animals were induced with hUC-MSCs once a week for four weeks for 42 d. The hUC-MSCs treatment induced downregulation of some pro-inflammatory genes (GFAP, Iba1, Il-1, TNF, IL-1b, and TNFa). Moreover, the treatment also downregulated IL-10, transforming growth factor-β and AMPA gene expression. The authors reported a modulation in the microglia M1/M2 polarization balance and a decrease in neuroinflammation involving complement C3 molecules, specifically in the C3a-C3aR pathway.

Therapy efficacy using BMMCs-derived exosomes in rats with depression induced by corticosterone treatment was performed by Guo *et al*[93]. The exosome therapy upregulated miR-26a microRNA, increased hippocampal tissue proliferation, and suppressed apoptosis in depressive-like rats. Treatment decreased oxidative stress and inflammation by inducing high superoxide dismutase antioxidant enzyme levels and decreasing lipoperoxidation, TNFa, and IL-1β levels in both serum and hippocampus.

Another study administered natural killer (NK)-cell-derived exosomes carrying miR-207, capable of inhibiting the NF-κB signaling pathway in astrocytes. This exosome treatment was effective in diminishing depressive symptoms in mice submitted to CMS and decreased the levels of IL-1b, IL-6, and TNFa released by astrocytes. The critical element of the exosome effect was the presence of the miR-207 molecule. When NK-cells were transfected with miR-207 inhibitor and exosomes were produced by and injected in astrocytes, the impact on IL-1b, IL-6, and TNFa levels was no longer observed[94].

CLINICAL TRIALS IN DEPRESSIVE PATIENTS

The results from different experimental studies strongly support the potential therapeutic use of stem cells in treating depression. However, while data from experimental models have shown beneficial effects in depression, gaps remain to be explored. Further studies are needed to clarify whether any MSCs type could be as effective and safe as an antidepressant therapy. For example, MSCs from the bone marrow have the best potential to treat depression, considering the significant data regarding them. However, ethical problems are to be considered when it comes to autologous transplants that require surgical intervention to obtain these cells. Moreover, allogeneic cell transplantation could be an acceptable clinical strategy. However, further studies are needed to assess the safety of using these cells from donors with a different genetic background than the patient.

In addition, further studies are needed to establish the optimal dose, administration route, and fundamental mechanisms of action. The translation ability of such experimental models to the target human population, possibly composed of refractory and polypharmacy patients, merits further discussion. For instance, previous efforts with several compounds that passed through animal studies with promising results have failed in clinical trials, partially due to the poor validity of such models to represent the target patient population[95].

Due to these gaps, the first clinical trials involving cell-based products or exosomes to treat depression have been registered to international platforms. At Clintrial.gov, the keywords "depression," "depressive disorder," and "cell therapy" were used to perform the search. This research led us to find four registered clinical studies involving the use of MSCs as a treatment for patients with depression. Currently, four clinical studies (phases 1 and 2) are under evaluation for the safety, efficacy, and tolerability of the administration of MSCs and exosomes (Table 2). However, most of the results are not yet available, as these studies are still in the patient recruitment phase. Therefore, the results are anticipated to be published from these trials soon.

CONCLUSION

Cell therapy, through BMMCs or MSCs transplantation or the administration of cell products such as exosomes, may have a place in treatment-resistant depression. The

Table 2 List of registered cell-based clinical trials for treating depression

Study	Country	Target population	Product	Study design	Outcomes
NCT02675556	United States	Treatment-resistant depression; (n = 80)	Allogeneic MSCs; 10^8 cells single i.v. infusion; source not reported	Phase I, placebo-controlled 1:1	Incidence of any treatment-emergent serious adverse events; Reduction of Inflammation.
NCT03522545	United States	Treatment-resistant bipolar depression; (n = 30)	Allogeneic bone marrow-derived MSCs; dose not reported	Phase I, placebo-controlled	Change in depression as assessed by the MADRS Scale.
NCT03265808	United States	Alcohol use disorder and major depression; (n = 80)	Allogeneic MSCs; 10^8 cells single i.v. infusion; source not reported	Phase I/II	An incident of treatment emergent-serious adverse events
NCT04202770	United States	Refractory depression; anxiety disorders; neurodegenerative diseases; (n = 300)	Focused ultrasound and exosomes	Single group assignment	Beck depression inventory (BDI-II)

MSCs: Mesenchymal stem cells.

number of preclinical studies is still limited; therefore, further development of clinical trials is encouraged.

As technology and knowledge involving all aspects of cells or cell-based products develop, the easier it is to identify the best alternative (cells or exosomes) to try as an antidepressant treatment, the lower the costs and the more established the routines. A significant development should be expected to understand its potential and possible side effects better.

Despite the limited number of preclinical studies, many issues have not been identified, such as how long the antidepressant effect persists. It is a critical question that has consequences for the feasibility of these procedures as treatment. Because of the challenge that represents the treatment of resistant depression, the possibility of an effective treatment in this chronic, severe, and prevalent condition must be explored.

For this, a more significant number of clinical studies are needed to evaluate several open questions considering the variability of the effectiveness of the use of stem cells in the treatment of depression.

ACKNOWLEDGEMENTS

The authors would like to thank Miss Ana Pereira do Prado Lima, who produced and allowed the publication of the graphic schemes used in Figure 1 of this review and allowed its use.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 September 19; 11(9): 568-580

DOI: 10.5498/wjp.v11.i9.568

ISSN 2220-3206 (online)

MINIREVIEWS

Antiglutamatergic agents for obsessive-compulsive disorder: Where are we now and what are possible future prospects?

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Author contributions: Maraone A performed the majority of the writing, prepared the table; Tarsitani L and Pinucci I provided the input in writing the paper; Pasquini M designed the outline and coordinated the writing of the paper.

Conflict-of-interest statement: There is nothing to disclose.

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Manuscript source: Invited manuscript

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Abstract

Recent data suggest that obsessive-compulsive disorder (OCD) is driven by an imbalance among the habit learning system and the goal-directed system. The frontostriatal loop termed cortico-striatal-thalamo-cortical (CSTC) circuitry loop is involved in habits and their dysfunction plays an important role in OCD. Glutamatergic neurotransmission is the principal neurotransmitter implicated in the CSTC model of OCD. Hyperactivity in the CSTC loop implies a high level of glutamate in the cortical-striatal pathways as well as a dysregulation of *GABA* ergic transmission, and could represent the pathophysiology of OCD. Moreover, the dysregulation of glutamate levels can lead to neurotoxicity, acting as a neuronal excitotoxin. The hypothesis of a role of neurotoxicity in the pathophysiology of OCD clinically correlates to the importance of an early intervention for patients. Indeed, some studies have shown that a reduction of duration of untreated illness is related to an earlier onset of remission. Although robust data supporting a progression of such brain changes are not available so far, an early intervention could help interrupt damage from neurotoxicity. Moreover, agents targeting glutamate neurotransmission may represent promising therapeutical option in OCD patients.

Key Words: Obsessive-compulsive disorder; Antiglutamatergic agents; Glutammate; Early intervention; Neurophysiopathology; Duration of untreated illness

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Core Tip: In pathophysiology of obsessive-compulsive disorder (OCD), dysfunction of the cortico-striatal-thalamo-cortical (CSTC) loop could provoke an imbalance between goal-directed system and habit learning system. Glutamate is the principal neurotransmitter implicated in the CSTC model of OCD. Glutammate dysregulation and

Specialty type: Psychiatry

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 1, 2021
Peer-review started: March 1, 2021
First decision: July 15, 2021
Revised: July 25, 2021
Accepted: August 6, 2021
Article in press: August 6, 2021
Published online: September 19, 2021

P-Reviewer: Kar SK
S-Editor: Gong SS
L-Editor: A
P-Editor: Guo X

neurotoxicity seem to be correlated, thus, an early intervention and a reduction of duration of untreated illness appear central in treatment of OCD, as well as the use of glutamate-modulating drugs that could help to interrupt damage from neurotoxicity.

Citation: Maraone A, Tarsitani L, Pinucci I, Pasquini M. Antiglutamatergic agents for obsessive-compulsive disorder: Where are we now and what are possible future prospects? *World J Psychiatr* 2021; 11(9): 568-580
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/568.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.568

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a severe and debilitating neuropsychiatric condition that affects 2.5%-3.0% of the general population[1,2].

OCD usually occurs in childhood or adolescence[3] and is associated with important distress, disability and suicidality[4]. Conventionally, OCD is driven by irrational beliefs (obsessions) considered as the product of a cognitive bias (including overestimation of threat, increased personal responsibility and thought-action fusion) and compulsions, which are rational avoidance responses triggered by these irrational beliefs that form a coping mechanism to neutralize anxiety and reduce the likelihood that fears will be realized. Preceding DSM-5[5], OCD was considered an anxiety disorder: Anxiety symptoms are indeed commonly expressed by patients[6]. Nevertheless, anxiety is not essential for OCD diagnosis and the condition was considered to be more similar to other disorders, therefore OCD was moved to a separated section of DSM-5[7].

First-line treatments include cognitive behavior therapy (CBT) and pharmacological treatment with serotonin reuptake inhibitors (SRIs)[8]. Unfortunately, around 40% of patients with OCD do not achieve remission of their symptoms with these therapies [6]. Even when an alternate selective serotonin re-uptake inhibitor or clomipramine treatment is given, or when an atypical antipsychotic is added, a considerable portion of refractory patients (30%) remain with the diagnosis, which is associated with serious social disability, patient's and family's suffering as well as a high suicide rate [9]. To understand the mechanisms underlying the development of OCD, a variety of hypothesis have been proposed, one of which is a dysfunction of the serotonergic and dopaminergic systems[10]. More recently, different studies focused their attention on the role of the glutamatergic system in OCD pathology[11]. Glutamate is the principal neurotransmitter involved in cortico-striatal-thalamic circuits (CSTC)[12] and, according to recent hypotheses (CSTC model of OCD), it would seem implicated in the pathogenesis of OCD. Moreover, there is consensus among experts on the importance of early intervention in OCD patients to reduce the duration of untreated illness (DUI) as well as to reduce the 'toxic' effect of an extended DUI in OCD[13]. The first aim of this mini review is an overview of the role of glutamate in CSTC models of OCD and the use of antiglutamatergic agents. Moreover we propose an intervention on the DUI in order to optimize fundamental time, due to the supposed toxic damages, and subsequently an early use of antiglutamatergic agents. Therefore, an early intervention could be both reduce the toxic effect of an extended DUI and, if necessary, encourage early use of antiglutamatergic agents.

WHAT DRIVES THE NEUROPHYSIOPATHOLOGY OF OCD?

As previously mentioned, conventionally OCD is driven by obsessions, while compulsions would be a rational avoidance response triggered by irrational beliefs. Patients report that, despite the repetitive and ritualistic nature of such behaviors, which are unproductive and frequently without any purpose, they are unable to discontinue them.

Recent data[14,15] suggest that OCD is driven by interference in the balance between the habit learning system and the goal-directed system. The habit learning system is based on historical information, regardless of past rewards, and it can lead to behavioural rigidity even in the face of rapid changes in the environment; on the other

hand, the goal-directed system applies control over habits in light of changes, including changes in response to the evaluation of actions and outcomes. A neurocomputational study[16] found that OCD patients made choices mostly based on model-free (*i.e.*, habit) rather than model-based (*i.e.*, executive control) learning. It is difficult for patients with OCD to modulate their future behavior based on immediate feedback. Therefore, in light of these hypotheses, habit formation appears to be abnormal in patients affected by OCD. According to the contemporary habit hypothesis, compulsive behaviours would not be driven by irrational and intrusive thoughts, but would be the consequences of a deficit in the control over goal-directed actions, leading to amplified reliance on habitual thoughts.

Orbitofrontal and cingulate cortices and the caudate nucleus are involved in habit learning[17,18] and in goal-directed control[19-21]. The frontostriatal loop termed CSTC circuitry is involved in habits and there is consensus that dysfunction of these areas plays an important role in OCD[22-24]. Dysfunction of the CSTC could cause disruptions between the goal-directed system and habitual control[25], which would cause an overreliance on the latter. Neuroimaging studies have shown that dysfunction of these areas has been implicated in OCD, including structural abnormalities, altered brain activation and connectivity[22,26]. The hypothesis is that in patients with OCD, the hyperactivation or hyperconnection of CSTC leads to a uncontrolled positive feedback loop[24,27]. This would trigger the impulse to perform compulsions, which would in turn consolidate the habit of executing compulsions, increasing the need to perform them[10].

In line with this behavioural hypothesis, OCD has been removed from anxiety disorders in DSM-5 and placed into its own category of "obsessive-compulsive and related disorders".

STATE OF ART ABOUT THE USE OF ANTIGLUTAMATERGIC AGENTS IN OCD

Traditionally, OCD medications have targeted serotonergic pathways. SRIs are commonly administered to treat patients with OCD and although the exact mechanism of their action remains elusive, SRIs are considered to exert their effects by influencing the CSTC[28]. However, the proportion of non-responder patients suggests a role of other neurotransmitter systems outside of the serotonergic in the pathophysiology of OCD[10].

Glutamate is the principal neurotransmitter implicated in the CSTC model of OCD [12]. In the neuropathophysiology of OCD, a dysregulation of the glutamatergic signal within the cortico-striatal circuitry has been suggested, which would lead to a reduced concentration of glutamate in the anterior cingulate cortex on the one hand, and overactivity of glutamatergic signalling in the striatum and orbitofrontal cortex on the other[29]. Hyperactivity in the CSTC loop implies a high level of glutamate in the cortical-striatal pathways and a dysregulation of GABAergic transmission that could represent the pathophysiology of OCD[10]. Furthermore, both ionotropic and metabotropic glutamate receptors are located in the candidate brain circuits of OCD and have been virtually associated with every form of learning in the brain, including habit learning[14,30]. Additionally, several studies showed an increase in glutamate in the cerebrospinal fluid of OCD patients compared to controls[1,31,32]. Genetics studies have also found an association between glutamate genes and OCD[33-35]. A polymorphism encoding for *N*-methyl-D-aspartic acid receptor (NMDAR) has been associated with OCD in families[33].

In light of a possible role of glutamatergic signal dysregulation in OCD, it is possible to find in glutamatergic drugs candidates for the augmentation strategy of OCD's therapy. Glutamate-modulating drugs have shown promise as potential therapeutic agents in other psychiatric disorders with a high comorbidity with OCD such as depression, bipolar disorder and suicide[36-38]. Moreover, several studies suggested that neuromodulation techniques using noninvasive devices, such as transcranial magnetic stimulation (TMS), or invasive procedures, such as deep brain stimulation (DBS), could offer additional support for the CSTC model of OCD. Based on the results of a recent randomized controlled trials (RCT), the Food and Drug Administration approved deep TMS, for the treatment of OCD[39,40]. Also DBS, which involves implantation of electrodes that modulate specific brain function, is approved for treatment of refractory OCD[41]. The first trials on DBS for OCD were conducted in the 2003 by Gabriëls *et al*[42] showed that DBS targeted at striatal areas is effective and safe for patients with refractory OCD.

This background has motivated the interest in studying glutamate modulators in patients who are unresponsive to standard pharmacotherapeutic approaches. Several clinical studies were conducted to evaluate the effect of glutamate-modulating drugs in OCD, however, they differed significantly in terms of treatment resistance, comorbidities, age and gender of the patients[29].

In particular, some studies using memantine and riluzole reported promising benefits[43]. Other studies have explored the role of stimulants and nutritional supplements such as *N*-acetylcysteine (NAC) and glycine[44-46]. Glutamate-modulating RCT for refractory OCD are reported in Table 1. To be more precise we describe the principal studies reported in the literature:

Memantine

Memantine, a low-to-moderate affinity noncompetitive NMDAR antagonist[47] currently approved for the treatment of Alzheimer's disease, is used as an augmentative agent to SRIs in the treatment of moderate to severe OCD. Four RCTs [48-51] were conducted using memantine *vs* placebo as an adjunctive treatment to SRIs [48,50,51] or fluvoxamine[49]. In three of these, conducted on 40, 42 and 32 patients, respectively[48-50], the adjunction of memantine (in the target dose of 5-10 mg/d for 12 wk[48] or 20 mg/d for 8 wk[49] or 12 wk[50] showed a reduction in scores at the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). In the last RCT[51] conducted on 99 patients, the use of memantine (in the target dose of 10 mg/d for 8 wk) *vs* placebo and *vs* gabapentin did not lead to the reduction of Y-BOCS scores.

A recent review on the subject conducted by Marinova *et al*[29] concluded that memantine is the compound that most consistently showed a positive effect as an augmentation therapy in OCD. However, a critical letter[52], exposed some concern on this conclusion mainly due to some methodological gaps and because all four RCTs were conducted in the same geographic area. Andrade[52] concluded that, in the light of these limitations, it is still premature to recommend the use of memantine as an OCD augmentation therapy and that more studies are needed.

Amantadine

Amantadine, a weak noncompetitive NMDAR antagonist originally used in the treatment and prophylaxis of viral infections, has been used in the treatment of some neurological conditions including Parkinson's disease, dementia, multiple sclerosis, cocaine withdrawal, pain and depression[53-55]. In one RCT, conducted on 100 patients diagnosed with moderate to severe OCD[56] the use of amantadine *vs* placebo as an adjunctive treatment to SRIs, showed a significant effect on Y-BOCS compared to placebo.

Riluzole

Riluzole acts through voltage-gated ion channels modulating the outflow of glutamate and enhancing the reuptake of extracellular glutamate. It is approved for the treatment of amyotrophic lateral sclerosis and some data report benefit in the use of riluzole for depression and anxiety[57]. Three RCTs were conducted using riluzole *vs* placebo adjunctive to SRIs[58,59] or fluvoxamine[60]. Only one study, conducted on 50 patients [60], using riluzole at a final dose of 100 mg/d for 10 wk, showed a reduction in the Y-BOCS score; while the other two, conducted on 38[58] and 60 patients[59], respectively, both using riluzole at a final dose of 100 mg/d for 12 wk, did not lead to the reduction in the Y-BOCS scores.

Ketamine

Ketamine, a noncompetitive NMDA receptor antagonist, is approved for the treatment of depression. An RCT by Rodriguez and colleagues[61], conducted on 15 drug-free adults with OCD (intravenous infusions of ketamine 0.5 mg/kg *vs* placebo) reported significant improvement of OCD symptoms in patients that received ketamine *vs* placebo. This study was the first RCT that proved the effect of antiglutamatergic agents on OCD symptoms without the presence of an SRIs.

Glycine

Glycine is an amino acid, NMDA glutamate receptor agonist. Only one RCT[46] conducted on a sample of 24 patients with OCD used glycine augmentation (60 g/d for 12 wk) *vs* placebo. This study had a high dropout rate due to the adverse effects of glycine. However, nearly significant improvements in Y-BOCS scores were observed in evaluable patients.

Table 1 Glutamate-modulating randomized controlled trials for refractory obsessive-compulsive disorder

Ref.	Drugs	Adjunctive/ monotherapy	Subjects	Duration & dose	Results
Haghighi *et al*[48], 2013	Memantine	Adjunctive to SRIs	40 pt	12 wk. Dose: 5-10 mg/d	Significant reduction. Y-BOCS score
Ghaleiha *et al*[49], 2013	Memantine	Adjunctive to fluvoxamine	42 pt	8 wk. Dose: 20 mg/d	Significant reduction. Y-BOCS score
Modarresi *et al*[50], 2018	Memantine	Adjunctive to SRIs	32 pt	12 wk. Dose: 20 mg/d	Significant reduction. Y-BOCS score
Farnia *et al*[51], 2018	Memantine	Adjunctive to SRIs	99 pt	8 wk. Dose: 10 mg/d	No significant reduction. Y-BOCS score
Naderi *et al*[56] , 2019	Amantadine	Adjunctive to SRIs	100 pt	12 wk. Dose: 100 mg/d	Significant reduction. Y-BOCS score
Grant *et al*[59], 2014	Riluzole	Adjunctive to SRIs	60 pt	12 wk. Final dose: 100 mg/d	No significant reduction. Y-BOCS score
Pittenger *et al*[58], 2015	Riluzole	Adjunctive to SRIs	38 pt	12 wk. Final dose: 100 mg/d	No significant reduction. Y-BOCS score
Emamzadehfar *et al* [60], 2016	Riluzole	Adjunctive to fluvoxamine	50 pt	10 wk. Final dose: 100 mg/d	Significant reduction. Y-BOCS score
Rodriguez *et al*[61], 2013	Ketamine	Monotherapy	15 pt	Intravenous infusions dose: 0.5 mg/kg	Significant reduction. Y-BOCS score
Greenberg *et al*[46], 2009	Glycine	Adjunctive pharmacological or psychotherapeutic treatment	24 pt	12 wk. Dose: 60 mg/d	No significant reduction. Y-BOCS score
Afshar *et al*[44], 2012	N-acetylcysteine	Adjunctive to SRIs	48 pt	12 wk. Dose: 2.4 g/d	Significant reduction. Y-BOCS score
Sarris *et al*[68], 2015	N-acetylcysteine	Adjunctive to SRIs	44 pt	16 wk. Dose: 3 g/d	No significant reduction. Y-BOCS score
Paydary *et al*[45], 2016	N-acetylcysteine	Adjunctive to fluvoxamine	44 pt	10 wk. Dose: 2 g/d	Significant reduction. Y-BOCS score
Costa *et al*[69], 2017	N-acetylcysteine	Adjunctive to SRIs	40 pt	16 wk. Dose: 3 g/d	No significant reduction. Y-BOCS score
Ghanizadeh *et al*[70], 2017	N-acetylcysteine	Adjunctive to SRIs	34 pt	10 wk. Dose: 2.4 g/d	Significant reduction. Y-BOCS score
Li *et al*[71], 2020	N-acetylcysteine	Adjunctive to SRIs	11 pt	12 wk. Dose: 2.7 g/d	Significant reduction. Y-BOCS score
Esalatmanesh *et al*[75], 2016	Minocycline	Adjunctive to fluvoxamine	102 pt	10 wk. Dose: 200 mg/d	Significant reduction. Y-BOCS score
Kushner *et al*[78], 2007	D-cycloserine	Adjunctive to CBT	32 pt	125 mg	Significant reduction. Y-BOCS score
Wilhelm *et al*[79], 2008	D-cycloserine	Adjunctive to CBT	23 pt	100 mg	Significant reduction. Y-BOCS score
Farrell *et al*[80], 2013	D-cycloserine	Adjunctive to CBT	17 pt	25-50 mg	Significant reduction. Y-BOCS score
Andersson *et al*[81], 2015	D-cycloserine	Adjunctive to CBT	128 pt	12 wk. Dose: 50 mg	Significant reduction. Y-BOCS score
Mataix-Cols *et al*[82], 2014	D-cycloserine	Adjunctive to CBT	27 pt	50 mg	Significant reduction. Y-BOCS score
Storch *et al*[83], 2007	D-cycloserine	Adjunctive to CBT	24 pt	250 mg	No significant reduction. Y-BOCS score
Storch *et al*[85], 2010	D-cycloserine	Adjunctive to CBT	30 pt	25 mg	No significant reduction. Y-BOCS score
Storch *et al*[84], 2016	D-cycloserine	Adjunctive to CBT	142 pt	50 mg	No significant reduction. Y-BOCS score

RCT: Randomized controlled trials; OCD: Obsessive-compulsive disorder; SRIs: Serotonin reuptake inhibitors; CBT: Cognitive behaviour therapy; pt:

Patients; Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

Nicotine

Some studies have also suggested that nicotine acts by promoting glutamatergic transmission as well as by stabilizing the glutamatergic hyperactivity of the loop running from the orbitofrontal cortex to the cyngulate gyrus, the striatum and the thalamus[62-65]. Nicotine acts on the desensitisation of nAChRs by increasing both glutamatergic transmission and, transiently, *GABA*ergic transmission. In particular, nAChR on GABA neurons are more desensitized then those on the glutamatergic system. This would lead to a shift toward excitation, reducing inhibitory inputs[65]. According to these data and with the complexity of OCD's pathophysiology, nicotine can be considered as a possible add-on therapeutic option in OCD resistant subjects, due to its peculiar mechanism of action. Only one study[66] was conducted on 5 patients using nicotine. Patients who received nicotine reported a reduction in Y-BOCS scores, especially in the compulsive score. A recent systematic review on the efficacy of nicotine administration suggested the need to test nicotine use in OCD in a large RCT. However, such suggestion raises ethical issues related to nicotine administration for its potential addiction effect[67].

NAC

NAC is a glutamate-modulating drug acting through the inhibition of the synaptic glutamate release. Five RCTs were conducted on adults[44,45,68-70] and one on children[71] using NAC *vs* placebo as an adjunctive therapy to SRIs[44,68-71] or fluvoxamine[45]. In three studies, conducted on 48, 44, 34 and 11 patients, respectively [44,45,70,71], the use of NAC (in the dose of 2.4 g/d for 12 wk[44] or 2 g/d for 10 wk [45] or of 2.4 g/d for 10 wk[70] or 2.7 g/d for 12 wk[71] showed improvement in the severity of OCD symptoms. On the other hands, in two studies conducted on 44[68] and 40 patients[69], respectively, the use of NAC (in the dose of 3 g/d for 16 wk)[68, 69] did not lead to a reduction of OCD symptoms.

Minocycline

Minocycline is an antibiotic that crosses the blood-brain barrier and has a neuroprotective effect that decreases glutamate-induced neurotoxicity[72]. It is used in some neurodegenerative diseases such as amyotrophic lateral sclerosis and Parkinson[73, 74]. Only one RCT was conducted on 102 patients using minocycline (200 mg/d for 10 wk) *vs* placebo as an adjunctive treatment to fluvoxamine. The results showed a reduction in Y-BOCS scores in the group that received minocycline[75].

D-cycloserine

D-cycloserine is a partial agonist at the *N*-methyl-d-aspartate receptor in the amygdala and some data have suggested a role of this receptor in fear extinction. For this reason, it was hypothesized that d-cycloserine may increase the efficacy of exposure therapy, a component of CBT for anxiety and OCD[76,77].

Eight RCTs were conducted on OCD patients using d-cycloserine *vs* placebo as an augmentation treatment of CBT with exposure and response prevention. Among these RCTs, four studies, conducted on 32[78], 23[79], 17[80] and 128 patients[81], respectively, used d-cycloserine in doses of 25[82] to 125 mg[78] close to each CBT session, reporting a significant amelioration of OCD symptom. In the other four studies, conducted on 27[82], 24[83], 30[45] and 142[84] patients, respectively, used d-cycloserine in doses of 25[85] to 250 mg[84] close to each CBT session, but did not show any statistically significant improvement.

In light of such contrasting results, it is not yet possible to give a clear answer on the use of glutamate-modulating drugs in OCD.

Therefore, further randomized placebo-controlled trials in larger study populations are essential to draw definitive indications on the efficacy of the use of antiglutamatergic agents in OCD.

THE REASON WHY EARLY INTERVENTION COULD BE IMPORTANT FOR OCD

As we underline, glutamate neurotransmission plays a crucial role in the CSTC of

OCD[12]. Furthermore, glutamate is also implicated in neuronal plasticity, learning, and memory[86]. Dysregulation of glutamate levels may bring glutamate receptor hyperactivity or even excitotoxicity in neurons and, in pathological situations, glutamate could lead to neurotoxicity by acting as a neuronal excitotoxin[87].

In support of this hypothesis, neuroimaging studies found changes in multiple sites of age-related brain structures suggesting that OCD is characterized by complex and nonlinear neurophysiopathological mechanisms[88,89].

The hypothesis of the role of neurotoxicity in the neurophysiopathology of OCD is clinically related to the importance of early intervention for patients. Indeed, some studies showed that a faster onset in the treatment of OCD correlates with an earlier onset of remission[90]. On the contrary, late intervention is associated with increased comorbidity, disability, reduced treatment response and remission[91-93].

The DUI for OCD is very high compared to other mental disorders[94]. Most cases of OCD arise in childhood or adolescence[92] and symptoms are often ignored[95] extending the time for diagnosis (from 2 to 10 year) and consequently for starting treatment[92,96,97] with average DUI of two to three years[98,99]. Although there is a paucity of data to support a progression of such brain changes so far, it is assumed that early intervention, even with the use of glutamate-modulating drugs, could help to stop neurotoxic damage[13]. A crucial point may be the switch from a time-dependent neurotransmitter dysfunction to an irreversible structural damage. This may explain both refractory to SSRI and the unresponsiveness to anti-glutamatergic agents.

Identifying and confirming the efficacy and safety of new therapeutic approaches for OCD could also be very useful for early intervention in these patients. An international group of expert clinicians and scientists with extensive OCD experience are documenting the negative impact associated with the delayed treatment on clinical outcomes, suggesting the importance of a greater emphasis on targeted early intervention for OCD patients as is already is the case for psychotic disorders. Early intervention is more promising for reducing chronicity as well as the economic and social burdens associated with OCD.

CONCLUSION

The hypothesis of a hyperactive CSTC loop that implies a high level of glutamate in the cortical-striatal pathways and a dysregulation of *GABA*ergic transmission may represent the pathophysiology of OCD. Despite the effectiveness of SRIs in treating OCD, the treatment-resistant symptoms observed in 40% of patients present enormous clinical issues. The refractory to SRIs and the unresponsiveness to antiglutamatergic agents may be explained by a time-dependent neurotransmitter dysfunction, which may lead to an irreversible structural damage. There is a need to develop novel pharmacological strategies, which are not exclusively related to refractory subjects. If glutamate-neurotoxicity is extensively confirmed, the time from OCD onset will be the most important variable to take into consideration. In such a scenario, agents targeting glutamate neurotransmission may represent a promising treatment, especially in the case of a timely prescription.

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World J Psychiatr 2021 September 19; 11(9): 581-588

DOI: 10.5498/wjp.v11.i9.581

ISSN 2220-3206 (online)

MINIREVIEWS

The renin-angiotensin system, mood, and suicide: Are there associations?

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Author contributions: Sanches M and Teixeira AL equally contributed to the writing and revision of the manuscript; all authors have read and approve the final manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United States

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Abstract

Available evidence points to a possible role of the renin-angiotensin system (RAS) in the pathophysiology of mood disorders and suicide. We carried out a critical analysis of literature data regarding this role, with a focus on the proposed association between RAS dysfunction and suicidal behavior. Epidemiological, genetic, and biochemical findings are described, and the pathophysiological hypothesis aiming at explaining the possible relationship between RAS and suicide are discussed. Available findings do support the involvement of the RAS in the neurobiology of suicide, although the exact mechanisms underlying this involvement are still unknown.

Key Words: Renin-angiotensin system; Suicide; Mood disorders; Depression; Bipolar disorder

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Core Tip: This is a minireview on the proposed role of renin-angiotensin system dysfunctions in the pathophysiology of suicide.

Citation: Sanches M, Teixeira AL. The renin-angiotensin system, mood, and suicide: Are there associations? *World J Psychiatr* 2021; 11(9): 581-588

URL: https://www.wjgnet.com/2220-3206/full/v11/i9/581.htm

DOI: https://dx.doi.org/10.5498/wjp.v11.i9.581

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

Received: March 9, 2021
Peer-review started: March 9, 2021
First decision: May 13, 2021
Revised: June 29, 2021
Accepted: August 3, 2021
Article in press: August 3, 2021
Published online: September 19, 2021

P-Reviewer: Ben Thabet J, Kapritsou M, Yang L
S-Editor: Wu YXJ
L-Editor: A
P-Editor: Guo X

INTRODUCTION

Despite the large amount of research aiming at understanding its clinical, epidemiological, and neurobiological correlates, suicide remains a leading cause of death worldwide[1,2]. Data from the World Health Organization indicate that, during 2015, 800000 suicides took place worldwide, corresponding to 1.4% of premature deaths[3]. Suicide represents the second leading cause of death during the second and third decades of life, with more than 45000 deaths by suicide reported in the United States alone during 2016[4]. From a psychiatric and epidemiological standpoint, there is a strong association between suicidal behavior and psychiatric disorders, particularly mood disorders (unipolar depression and bipolar disorder). Approximately 50% of all completed suicides are associated with mood disorders, with a 20-fold increase in the risk of suicide among individuals suffering from depression or other mood disorders compared to healthy individuals[5-7].

In order to characterize the pathophysiology of suicide, most authors adopt a stress-diathesis model, according to which certain individuals with genetic vulnerability exhibit increased risk of suicidal behavior when exposed to external stressors or life events[8,9]. A large amount of evidence supports the involvement of neurobiological factors in the pathogenesis of suicidal behavior, although the search for suicide biomarkers has not yet produced consistent findings. In addition to abnormalities in the serotonergic system, the most consistent neurobiological findings associated with suicide are related to dysregulation in stress response and its downstream effects[10,11].

Over the last several years, the renin-angiotensin system (RAS) has been the object of great interest due to its possible involvement in the pathophysiology of mood disorders and suicide[12,13]. At a systemic level, the RAS plays an important role in blood pressure regulation and in the maintenance of body homeostasis. Furthermore, the existence of a brain RAS is well-established, with angiotensin-II receptors being found in brain areas involved in the processing of emotions, including the amygdala, the hippocampus, and the prefrontal cortex[14,15]. Evidence points to associations between increased RAS activity and depression, with angiotensin conversion enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) having been hypothesized as having protective and possibly therapeutic effects against mood disorders[12,16,17]. On the other hand, some epidemiological studies have raised concerns about possible associations between the use of medications targeting the RAS and increased risk of suicide. In particular, the results of a recent study pointing to the association between the use of angiotensin receptor blockers and suicide[18] have been discussed not only by the specialized literature but also in the mass media due to the potential implications and the widespread use of these medications in the treatment of hypertension and other cardiovascular conditions[19,20].

The current mini-review critically analyzes the putative relationships between the RAS, mood disorders, and suicide, in light of available evidence. Clinical and epidemiological data are discussed, in addition to considerations on the hypothesized neurobiological mechanisms involved in the interface between RAS and suicidal behavior.

MOOD DISORDERS AND THE RENIN-ANGIOTENSIN SYSTEM

Alterations in systemic markers of RAS activity among mood disorder patients have been reported, and studies have shown lower rates of depressive symptomatology among patients receiving angiotensin receptor antagonists and ACE inhibitors for the treatment of hypertension or diabetic nephropathy[13,17]. Further, improvements in depressive symptoms and interpersonal sensitivity among patients with diabetes type II using angiotensin receptor blockers have been observed[21].

Nevertheless, the relationship between RAS activity and mood disorders seems to be more complex, involving interactions among the RAS, inflammation, the hypothalamic-pituitary-adrenal (HPA) axis, and mood regulation. A large amount of evidence supports the notion that increases in RAS activity result in the activation of the HPA axis. For example, stimulation of the angiotensin II receptor type 1 (AT1) in the hypothalamic paraventricular nucleus brings about increases in the release of corticotrophin releasing hormone, ultimately contributing to HPA axis hyperactivation in animal models[22]. Furthermore, certain variants of the *ACE* gene, such as rs4291 and the D allele, related with higher ACE serum activity and increased HPA axis activity, have been found to be associated with depressive disorders[23,24].

In addition, there are multiple interactions among RAS, inflammation, and psychiatric disorders[13,15,25,26], with strong evidence from *in vitro* and *in vivo* studies supporting the effects of angiotensin II as a potent pro-inflammatory agent[27]. Recently, it was hypothesized that the RAS is composed by two arms with opposite actions in terms of inflammatory activity and effects on the pathophysiology of mental illnesses. The first arm, composed by ACE, angiotensin II, and AT1, shows pro-inflammatory effects, while the second arm, comprised of ACE2, Ang (1-7), and angiotensin receptor type II (AT2) seems to have anti-inflammatory effects and a putatively protective effect against the development of neuropsychiatric conditions[15]. Moreover, decreases in angiotensin II activity induced by ACE inhibitors or angiotensin II receptor blockers have been found to significantly reduce the concentrations of inflammatory mediators such as IL-6, TNF-α, and CRP, and have been found to be of benefit for patients with inflammatory diseases[27-29].

Furthermore, it is not yet clear whether different patterns of associations with the RAS are found across distinct subtypes of mood disorders. Studies specifically examining the role of the RAS in bipolar disorder are scant and the cyclic nature of that condition adds an extra layer of complexity to the investigation of RAS-related abnormalities and their involvement in the pathophysiology of BD different mod states. Our group recently described decreased ACE levels among individuals with BD in acute mood states (irrespective of type of mood episode) when compared to controls, but no significant correlations were specifically found between ACE levels and depressive or manic symptoms[14]. Based on findings from animal models, it has been proposed that candesartan, an angiotensin receptor antagonist, may have antimanic-like properties[16] but, given the proposed antidepressive properties of RAS modulators, as described above, a possible the association between increased RAS activity and mania seems to be of difficult interpretation. Of notice, one anecdotal report described associations between ACE use and the onset of acute mania[30].

In summary, even though the exact neurobiological mechanisms underlying the relationship between RAS and mood are not yet completely clarified, there is strong evidence suggesting that the relationship in question is mediated by possible effects of the RAS on the HPA and on inflammatory processes. That is of particular importance when analyzing possible interactions between RAS and suicide, as discussed in the next section.

THE RENIN-ANGIOTENSIN SYSTEM AND SUICIDE

Epidemiological data

The first studies looking at possible relationships between the RAS and suicide were published in the later 1990s and early 2000s. For example, in a cross-sectional ecological study carried out in 152 municipalities in Sweden[31], the use of ACE inhibitors by patients with hypertension, in contrast with calcium channel blockers, was not associated with increased suicide rates. In another study, which utilized data from a 5-year Danish cohort comprised by 58529 subjects receiving beta blockers, calcium channel blockers, or ACE inhibitors[32], there was a slight, non-significant elevation in the standardized mortality ratio (SMR) for suicide among patients on ACE inhibitors [SMR: 1.2; 95% confidence interval (CI): 0.7-1.8]. Similarly, in a subsequent nested case-control study analyzing 743 cases of completed suicide and 14860 matched controls [33], ACE inhibitors were not significantly associated with suicide (OR: 1.11; 95%CI: 0.68-1.83). In the same study, based on five of the cases exposed, current use of ARBs was associated with elevations in suicide risk (OR: 3.52; 95%CI: 1.33-9.30). Nonetheless, when a subsequent restricted analysis (which excluded subjects with a history of psychotropic drug use) was performed, the associations between current ARB use and risk of suicide became non-significant (OR: 3.32; 95%CI: 0.93-11.8).

While in the studies mentioned above the possibility of increased suicide risk among individuals receiving RAS medications was analyzed in a broader context, *i.e.*, studies of the possible associations between suicide and use of cardiovascular drugs, more recent studies have specifically focused on the hypothesis that ACEs and ARBs could be related to elevation in the risk of suicide. Mamdani *et al*[18] carried out a population-based nested case-control study involving 964 individuals aged 66 years and older who died by suicide and 3856 matched controls. Data were obtained from administrative claims databases in Canada, over a period of 20 years (1995 to 2015). The authors reported significant associations between the use of ARBs (but not ACE inhibitors) and higher suicide risk (adjusted OR: 1.63; 95%CI: 1.33-2.00). Of notice, the findings remained significant even after individuals with a previous history of self-

harm were excluded from the analysis (OR: 1.60; 95%CI: 1.29-1.98). However, data on past history of substance abuse and personality disorders among cases and controls was not available.

On the other hand, in a similarly designed study using data from the Veterans Health administration in the United States[34], no significant associations between the use of ARBs or ACE inhibitors and elevations in suicide risk were found. Data of 1309 cases of completed suicide and matched 5217 controls, collected between 2015 and 2017, were included in the analysis. The adjusted suicide OR for ARBs was 0.98 (95%CI: 0.83-1.16), whereas the crude suicide OR for ARBS *vs* ACE inhibitors was 0.966 (95%CI: 0.828-1.127).

Moreover, a study using information from the National Health Insurance Research Database in Taiwan looked at associations between ARB use and suicidal behavior [35]. The authors conducted a retrospective population-based cohort study and estimated the rates of suicide attempts among ARB users, propensity-score matched with non-users. The suicide attempt rates were significantly lower among ARB users than among non-users (adjusted hazard ratio: 0.48; 95%CI: 0.26-0.87), and a Kaplan Meyer survivor analysis showed a lower cumulative incidence of suicide attempts among ARB users compared to non-users.

Last, Köhler-Forsberg *et al*[36] recently performed a register-based nationwide cohort study comparing individuals started on a selective serotonin reuptake inhibitor (SSRI) with and without concomitant use of a RAS medication. Both groups were propensity-score matched and were followed over a period of up to three years. Individuals in the group receiving SSRIs plus RAS medications showed reduced risks for psychiatric hospital contacts and lower mortality rates when compared to those receiving only SSRIs. Differences between groups in terms of suicidal behavior were not statistically significant (hazard rate ratio: 1.06; 95%CI: 0.79-1.42).

In summary, available data from epidemiological studies suggesting relationships between use of RAS medications and suicide are inconsistent, with important variations in terms of the direction of such interactions (increased *vs* decreased risk of suicide in association with RAS medications) and of possible differences between different classes of RAS medications (ACE inhibitors and ARBs). Additionally, it is not totally clear, in light of current available evidence, whether these relationships, if present, are modulated by other factors, such as previous psychiatric history, age, and other demographic data. Methodological issues might explain at least part of the discrepant findings across different studies, as explained in the discussion section.

Biological findings

To date, the neurobiological evidence analyzing the relationship between RAS activity and suicidality is scant. One early study described increases in ACE activity in the substantia nigra of individuals who completed suicide[37]. More recently, Hallberg *et al*[38] looked at the levels of renin and aldosterone among depressive disorder patients [major depressive disorder (MDD), dysthymic disorder, and adjustment disorder] with and without a history of suicide attempt, as well as healthy controls. Serum levels of aldosterone were significantly lower among MDD patients with a history of suicidal behavior when compared to the other groups. Interestingly, no association between history of suicide attempt and aldosterone levels was found among individuals with other depressive disorders, and MDD patients without a history of suicidal attempt were similar to healthy controls in terms of their aldosterone levels. Together, these findings suggest that decreased aldosterone could represent a marker of suicidality among patients with MDD.

Given the evidence suggesting that increased RAS activity may be associated with depressive symptomatology, Hong *et al*[39] investigated the distribution of the ACE gene insertion/deletion (ACE I/D) polymorphism among major depressive disorder patients with and without a history of suicide attempts. The authors hypothesized that D allele (which has been associated with increases in RAS activity compared to I allele) would be found at a higher frequency among suicide attempters. No statistically significant differences between groups regarding the polymorphisms in question were found. Nevertheless, other studies have reported positive findings regarding the association between the ACE D allele and suicidal behavior. In one of them[40], significant differences in the distribution of ACE I/D polymorphisms between suicide attempters and non-attempters were reported, with higher frequencies of the DD genotype among attempters. Furthermore, the results of two other unrelated case-control studies were jointly reported by Sparks *et al*[41]. In the first study, 64 subjects who completed suicide were compared to 90 controls, with higher rates of the ACE DD allele in the completed suicide group. Among individuals carrying the DD allele, the OR for completed suicide was 2.4 (95%CI: 1.2-4.8) when compared to II and ID

bearers. In the second study, 588 patients hospitalized following a suicide attempt were compared to 639 healthy controls. While statistically significant higher frequencies of the D allele were reported among cases, differences between groups with respect to genotype frequencies were not statistically significant.

On the other hand, a 2006 study carried out in Japan[42] looked at possible associations between suicide and functional polymorphisms in ACE gene and three other RAS-related genes: angiotensin, angiotensin type-1 receptor, and GNB3. A total of 166 completed suicides and an equal number of unrelated controls were included in the analysis. While there were no statistically significant differences between groups with regards to genotype distributions, the I allele frequency of the ACE insertion/deletion (ACE I/D) polymorphism was significantly higher in the complete suicide group, specifically in males. The risk of suicide among male individuals with the I allele was found to be more than 50% higher (OR: 1.55, 95%CI: 1.07-2.26). Furthermore, among male I/I homozygotes, the risk of suicide was estimated as more than 80% higher (OR: 1.84, 95%CI: 1.08–3.12). Even though the results in question did not remain positive after correction for multiple comparisons, since the I allele is associated with low ACE levels, these results suggest that decreased RAS activity could contribute to elevations in suicide risk. These findings were partially replicated by Fudalej *et al*[43], who described an increased frequency of the ACE I allele among male victims of suicide compared to male controls (OR: 1.69, $P < 0.006$).

DISCUSSION

The evidence outlined above points to associations between RAS activity and suicide risk. Despite the great variability of the results, the most replicated findings suggest a higher risk of suicidal behavior among carriers of the ACE gene DD allele. Results from epidemiological studies are less consistent, with different patterns of association between suicidal behavior and use of RAS medications.

Several theories aiming at explaining the putative pathophysiological mechanisms responsible for the relationship between RAS activity and suicidal behavior have been formulated. One of the most frequently discussed hypothesis is based on the described interactions between RAS, stress regulation, and the HPA axis. This is of particular importance given the recent attention given to the role of HPA axis hyperactivation as a possible diagnostic-independent suicide biomarker[44]. Elevated HPA activity contributes to the development of depression, which, on its turn, is associated with higher risks of suicide. Therefore, this mechanism provides a simple and straightforward explanation for the hypothesized relationship between increased RAS function and suicide risk, as suggested by the genetic studies describing higher rates of suicide among ACE D allele carriers (who show increased ACE activity) and the epidemiological data pointing to lower risk of suicidal behavior in individuals receiving RAS medications.

On the other hand, there are also findings indicating that suicidal patients with depression, in comparison to non-suicidal ones, might show decreased HPA response and lower cerebrospinal fluid levels of CRH[45,46]. In consonance with the results of the studies pointing to correlations between suicide and the ACE I allele, associated with decreased ACE activity, and the description of reduced aldosterone levels among suicidal MDD patients, those findings suggest that, in fact, decreased RAS activity could contribute to elevation in the risk of suicide.

How to explain these apparently conflicting findings? It has been proposed that the relationship between RAS activity and HPA axis might actually be bidirectional, with the RAS system not only having direct effects in the regulation of the HPA axis but also suffering downstream effects of increased HPA activity[14]. In rats, the expression of angiotensin 1 receptors seems to increase as a result of stress exposure[22], and this effect might be mediated by HPA axis-modulated increases in cortisol levels. As demonstrated in another animal study, the number of angiotensin 1 receptors in the brain was significantly decreased by adrenalectomy, and this effect was reversed by the administration of corticosteroids[47]. Therefore, one can hypothesize that, in some suicidal individuals, elevations in the HPA axis could bring about reductions in angiotensin 1 receptor expression which could lead to increases in the circulating brain levels of angiotensin II and, in its turn, produce compensatory reductions in ACE levels and downstream RAS activity through negative feedback. The exact mechanisms involved in this putative self-regulatory interaction between HPA axis and RAS are still poorly understood, and it is not clear either, in light of available evidence, whether the different ACE gene polymorphisms described above could have

distinct impacts on the modulation of this interaction.

Moreover, the different case-control studies reported show different patterns of association between use of RAS medications and suicide risk. While the study by Mamdani *et al*[18] pointed to increased risk of suicide associated with the use of ARBs but not ACE inhibitors, other studies failed to identify increases in suicide risk among ARB users. The study in question has received some criticism with respect to certain methodological limitations, some of which related to the age range of the subjects included in the study (which included only individuals 65 years and older), the lack of better characterization of the groups in terms of their psychiatric history and comorbidity, and other limitations inherent to case-control studies[19]. Still, one possible explanation to the reported elevation in suicide risk associated with ARBs but not ACE inhibitors involves interactions between RAS and substance P. Evidence indicates that the RAS plays a role in the regulation of substance P, with increases in ACE activity resulting in correspondent angiotensin II-mediated elevations in substance P levels in the brain[24,34,48]. The D allele of the ACE gene, which is associated with a higher risk of affective disorders, is correlated with elevated levels of substance P in the basal ganglia and substantia nigra[24]. Further, increases in substance P activity seem to be associated with anxiety and mood symptomatology, and substance P receptor antagonists have been investigated as for their possible antidepressant properties[49,50]. It has been proposed that ARBs use could result in compensatory elevations in the circulating levels of angiotensin II, leading to increases in the levels of substance P and, consequently, with elevations in the risk of suicide.

CONCLUSION

While available evidence does support the existence of an association between RAS dysfunctions and suicide, there are inconsistent findings with respect to the direction of this association. In other words, in contrast to the findings strongly suggesting that a hyperactive RAS seems to play a role in the pathophysiology of mood disorders, in the case of suicidal behavior, it is not possible to pinpoint whether increased or decreased RAS contributes to elevations in the risk of suicide and even if a direct cause-and-effect relationship does exist. Moreover, it is not yet clear whether this relationship, if present, corresponds an indirect effect, modulated by a putative role of RAS dysfunctions in the development of mood disorders and other psychiatric conditions (which would, by default, bring about increases in the risk of suicide) or results from an independent effect of RAS dysfunctions on the neurobiological mechanisms associated with suicide. Given the importance of suicide and the urgent need for interventions aiming at improving its prevention, a better understanding of the involvement of the RAS in its pathophysiology would have profound implications for psychiatry, neuroscience, and public health.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 September 19; 11(9): 589-604

DOI: 10.5498/wjp.v11.i9.589

ISSN 2220-3206 (online)

MINIREVIEWS

Cognitive attentional syndrome and metacognitive beliefs as potential treatment targets for metacognitive therapy in bipolar disorder

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Author contributions: All authors participated sufficiently in the manuscript to take public responsibility for its content; all authors provided substantial contributions to the conception and design of the manuscript, contributed to drafting and revising it, and provided final approval of the version that was submitted.

Conflict-of-interest statement: No conflicts of interest.

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Abstract

Most treatment guidelines emphasize the use of psychotropic drugs for both the acute and maintenance treatment of bipolar disorder (BD). However, relying only on psychotropics without adjunctive psychosocial interventions may be insufficient in treating patients with BD. Given its unique view in the explanation of psychopathological states, metacognitive therapy (MCT) might be helpful for BD. Metacognitive theory posits that psychopathology is a result of the cognitive attentional syndrome (CAS) and that it is influenced and maintained by dysfunctional metacognitive beliefs, perseverative thinking, attentional biases, and dysfunctional coping strategies. In this review, literature data regarding these areas in BD are examined. Studies suggest that perseverative thinking might be among the emotion regulation strategies endorsed in individuals with BD. Regarding attentional biases, literature data show that state-dependent, mood-changing attentional biases and a ruminative self-focused attention are present. Studies also suggest that cognitive self-consciousness is higher in BD compared to controls. It is seen that maladaptive coping strategies are frequently reported in BD, and that these strategies are associated with depression severity, negative affect and relapse risk. Studies focusing on dysfunctional metacognitive beliefs in BD reported that individuals with BD had higher scores for negative metacognitive beliefs, self-consciousness, need to control thoughts, and a lack of cognitive confidence. Also, dysfunctional metacognitive beliefs were associated with depressive symptomatology. These findings suggest that the components of CAS

Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Turkey

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 14, 2021
Peer-review started: March 14, 2021
First decision: June 5, 2021
Revised: June 16, 2021
Accepted: August 13, 2021
Article in press: August 13, 2021
Published online: September 19, 2021

P-Reviewer: Scaini S, Shiina A
S-Editor: Yan JP
L-Editor: A
P-Editor: Guo X

and dysfunctional metacognitive beliefs are evident in BD. For a subgroup of patients with BD who fail to respond to evidence-based psychopharmacological and adjunctive psychotherapeutic interventions, MCT might be an alternative way to consider as a treatment option. In conclusion, taken the available data together, we propose a sequential treatment protocol for BD, mainly based on the MCT treatment plan of depressive disorders.

Key Words: Attentional biases; Bipolar disorder; Dysfunctional coping; Metacognition; Metacognitive therapy; Perseverative thinking; Threat monitoring

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Core Tip: Relying only on psychotropics without adjunctive psychosocial interventions may be insufficient in treating patients with bipolar disorder (BD). Given its unique view in the explanation of psychopathological states, metacognitive therapy (MCT) might be helpful. In this review, literature data regarding dysfunctional metacognitive beliefs, perseverative thinking, attentional biases, and dysfunctional coping strategies in BD are examined. Findings suggest that dysfunctional metacognitive beliefs are evident in BD. Taken the available data together, we lastly propose a sequential treatment protocol for BD, mainly based on the MCT treatment plan of depressive disorders.

Citation: Batmaz S, Altinoz AE, Sonkurt HO. Cognitive attentional syndrome and metacognitive beliefs as potential treatment targets for metacognitive therapy in bipolar disorder. *World J Psychiatr* 2021; 11(9): 589-604
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/589.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.589

INTRODUCTION

Treatment of bipolar disorder (BD) is complex. Most treatment guidelines emphasize the use of psychotropic drugs for both the acute and maintenance treatment of BD[1-4]. However, psychotropics alone without adjunctive psychosocial interventions does not come close to meeting the outcome expectations of providers and patients[5]. Therefore, the effectiveness of many psychotherapeutic interventions has been investigated[6-9]. A recent meta-analysis concluded that adjunctive psychotherapy that emphasizes illness management strategies and enhances adaptive coping skills may benefit individuals with BD[10]. Unfortunately, current psychotherapies also suffer from many shortcomings, and many areas of psychotherapy for BD still need to be explored[11]. Developments in the understanding of psychopathology beyond the current and conventional approaches may help clinicians to provide more efficacious and acceptable treatments to individuals with BD. Given its unique view in the explanation of psychopathological states, metacognitive therapy (MCT) may offer one of these advanced approaches.

MCT AND THEORY

Metacognitive theory posits that psychopathology results from cognitive attentional syndrome (CAS)[12], which involves perseverative thinking styles, attentional biases, and dysfunctional coping strategies. The theory also proposes that CAS is influenced and maintained by dysfunctional metacognitive beliefs. As a treatment modality, MCT targets CAS and metacognitive beliefs to break the vicious cycle in which the patient is mentally stuck.

Perseverative thinking style may manifest as worry and rumination. While worry is generally defined as asking "what if" questions about future events, rumination mostly involves asking "why" questions about past events. These forms of extended thinking cause the person to be trapped in an inescapable thought process. Persev-

erative thinking increases the negative emotional consequences of the situation at hand, takes long periods of time, and does not aid those who engage in it in solving the problems they faced in the first place. Attentional biases are presented as fixed attention on threats (threat monitoring) or focused attention on the self. As a result, those with attentional biases become more aware of their internal experiences, many of which are negative in essence, which creates a vicious cycle in which they begin to believe that their feelings reflect the reality and that feeling that particular way is appropriate. The more focused they are on their thoughts, feelings, or sensations, the greater their reactions to such stimuli. Focusing on threat cues also increases the likelihood that they will feel distressed by them. Dysfunctional coping strategies, such as thought suppression, avoidance, or substance use, are applied to reduce the feelings of distress, but conversely, those strategies backfire and make the situation worse[12]. Components of CAS are maintained by underlying metacognitive beliefs, which may be either positive or negative. Positive metacognitive beliefs generally relate to the advantageous aspects of CAS, whereas negative metacognitive beliefs mainly center on the uncontrollability of perseverative thinking or the negative consequences of engaging with the CAS[12].

Regarding depressive disorders, metacognitive theory suggests that the person, in response to negative internal experiences—mostly negative automatic thoughts or beliefs—decides to focus attention specifically to dwell on the past or on some real or imagined personal failure. This overthinking pattern may also involve focusing on worries about what may happen in the future, like the recurrence of a new depressive episode. Consequently, this selective and self-referential attentional process extends the negative thinking style, eventually forming a trap from which the person cannot escape. At the same time, the theory also proposes that the person holds some positive beliefs about the benefits of extended thinking, which may be associated with a belief that rumination will help to solve problems or to identify the root cause of negative feelings. On the other hand, the person may also believe that the excessive ruminating is uncontrollable and that it may harm his or her physical or mental well-being or result in social exclusion[13]. In addition, the person with a depressive disorder will engage in dysfunctional, backfiring coping behaviors, which may include inactivity, social withdrawal, alcohol and substance use, repetitive mood- and energy-level checking, self-harming or suicidal behaviors, avoidance of feelings and thoughts, efforts at thought control, and so on. Such beliefs about rumination and such coping behaviors are thought to be the underlying maintenance factors in depressive disorders[12].

To this end, for those with depressive disorders, an MCT therapist first identifies a trigger thought, which generally corresponds to the ruminative thinking style of the patient, and then tries to eliminate, or at least limit, the amount of time the patient spends on rumination. The therapist also works with the patient to find ways to abandon any attentional biases, which generally consist of self-referential, self-focused attention and threat monitoring, and ways to stop engaging with any dysfunctional, backfiring coping strategies. In MCT, additionally, the therapist focuses on identifying and reality-checking any positive and negative metacognitive beliefs so that any maintaining factor is targeted and eliminated[13].

A recent meta-analysis concluded that MCT may be at least as effective as cognitive behavioral therapy for treating depressive disorders[14]. Whether MCT may also be effective for treating BD has yet to be explored. Currently, the literature on the effectiveness of MCT for treating BD is minimal. In the only case series on the application of MCT in individuals with BD type II published thus far, MCT was found to effectively make clinically significant improvements within 7-12 therapy sessions[15].

This review aimed to focus on any developments in the literature that highlight factors associated with the metacognitive model of BD therapy and to propose a theoretical framework for applying MCT for BD. We begin this paper with a summary of what is already known and reported in the literature and identify where the gaps in the research lie, and we end with a theoretical suggestion for the application of MCT for BD patients.

CAS IN BD

Since MCT is transdiagnostic in its approach to psychopathology, CAS in BD also consists of perseverative thinking, attentional biases, and dysfunctional coping strategies. Dysfunctional metacognitive beliefs are the underlying maintenance factors in BD, as they are in any other psychiatric disorder. Some examples of CAS and

dysfunctional metacognitive beliefs that may be encountered in patients with BD are presented in Table 1.

PERSEVERATIVE (EXTENDED) THINKING (RUMINATION AND WORRY)

Adaptive and maladaptive emotion regulation strategies have been defined as transdiagnostic processes[16]. Two recent articles discussed reviews that examined how individuals with BD try to regulate their internal experiences[17,18]. These articles stated that perseverative thinking may be among the emotion regulation strategies endorsed in individuals with BD and in individuals at risk for mania. Although many other forms of perseverative thinking exist, most studies have focused on rumination and, to a lesser extent, on worry in BD patients.

Two earlier reviews on rumination related to BD suggested that rumination, which was present in all phases of the disorder, was independent of the mood state of the individual, although closely related to it. In addition to depressive rumination, which was commonly associated with depressive phases in both major depressive disorder and BD, individuals with BD additionally and uniquely ruminated on positive affect, which can influence the triggering of new episodes. Rumination was also found to have negative consequences on cognitive and executive functions, most importantly, inhibitory control[19,20]. Another review proposed that spontaneous thoughts can predict depressive episodes and BD *via* the mediation of rumination, particularly if it is self-focused, past-focused, or associated with abstract processing and if cognitive control is reduced. Such spontaneous thoughts may be relevant for future BD episodes if they are characterized by goal-striving and if they are frequent, self-centered, and focused on grandiose successes[21].

A recent meta-analysis on rumination associated with BD revealed no significant differences in rumination in general or in depressive rumination between individuals with BD and those with major depressive disorder. However, individuals with BD reported ruminating more often on positive affect than those with major depressive disorder. The results also demonstrated that, albeit non-significant, when comparing BD subtypes with major depressive disorder, a tendency toward more rumination in general in favor of BD type I was observed. This tendency was not observed for individuals with BD type II[22].

Studies published since, or not included in, this meta-analysis have demonstrated similar findings regarding the frequency of rumination and maladaptive emotion regulation strategies in BD patients. Interestingly, increased rumination was found to be a mediator between anxiety levels and suicide behaviors in individuals with BD[23, 24]. Negative rumination has also been proposed as a mediator between traumatic distress and hypomania levels[25]. Another study comparing euthymic BD individuals with healthy controls indicated that both subtypes ruminated more frequently but that they did not worry more. The researchers of that study also suggested that depressive rumination may be a trait-specific feature of BD[26]. Trait rumination—specifically, rumination on positive emotions—was reported to be a characteristic of individuals with remitted BD[27]. Based on a study in which individuals with BD types I and II were compared with individuals with major depressive disorder and healthy controls, the researchers reported that individuals with both BD subtypes ruminated more frequently than the healthy controls did but not more than the individuals with unipolar depression[28]. Further, in a study for which individuals with both subtypes of BD who were either in an acute depressive episode or in remission were recruited, the participants were found to score higher on the rumination scale than the healthy controls. In this study, however, individuals with BD did not differ significantly from the healthy controls on self-focused positive rumination, and they even scored significantly lower than the control subjects on emotion-focused positive rumination [29]. An earlier study with a controversial result claimed that rumination was more evident in individuals with BD in the remitted phase than in the depressive phase[30]. The authors of another research paper concluded that the processes of dampening and emotion-focused positive rumination played important roles for individuals with BD [31]. Additional research focusing on positive rumination in individuals with BD revealed that these individuals endorsed more responses focused on positive affect and that these responses were explained by the level of hypomanic symptoms[32-34]. Unexpectedly, depressive rumination was also associated with hypomania severity in previous reports[35-38]. Moreover, depressive rumination was associated with lower self-esteem scores in individuals who were considered at high risk for BD[39].

Table 1 Examples of the components of the cognitive attentional syndrome and dysfunctional metacognitive beliefs in bipolar disorder

	Depressive phase	Hypo/manic phase
Perseverative thinking	"Why am I so depressed? What is the point in living any more? What is the root cause of my depression? Why can't I just snap out of this feeling?"	"I can do whatever I like, I have never been stronger! I feel so great, and this feeling must last forever."
	"What if I never get better? Will I always feel like this? What if I have a recurrence?"	"How dare they think that I should not be doing the things I want to? Nobody has the right to tell me what I am allowed to do."
		"What if my mood deteriorates? What if I start to feel depressed again? Will my health never be like everyone else's?"
Attentional biases and threat monitoring	Constant mood monitoring, self-focused attention, focusing on any changes in depressive symptomatology, checking energy levels, body scanning for early warning signs of recurrence	Constant mood monitoring, self-focused attention, focusing on any changes in hypo/manic symptomatology, checking energy levels, body scanning for early warning signs of recurrence
Dysfunctional coping strategies	Thought control, inactivity, self-harm, alcohol/substance use, emotional avoidance, social withdrawal	Thought control, hyperactivity, impulsivity, alcohol/substance use, emotional overindulgence, increased social interaction
Negative metacognitive beliefs	"Rumination is uncontrollable. Worrying will harm me. If my energy level changes during the day, this means that I am about to get depressed."	"Rumination is out of my control. Worrying too much might harm me. I have a broken brain. My genes are responsible for my disorder, and there is no way to cure it."
	"My friends will leave me because of my never-ending rumination."	"I can not form stable relationships because of my bipolar disorder. This has ruined my life."
Positive metacognitive beliefs	"Rumination will help me identify the cause of my depression. Worrying keeps me prepared for any unwanted consequences. Checking my mood will tell me when I am at risk for depression."	"Thinking about my positive mood will make my day better. The more time I spend time on my heightened energy, the less probable that I fall back to my depression. Worrying that I may experience a relapse will help me identify any early warning signs."

The subject of worry in BD patients has not attracted the same amount of scholarly attention as rumination. Nevertheless, individuals with BD type I and II were found to worry more frequently than healthy controls but not more than individuals with unipolar depression[28]. Similar results indicating individuals with BD worried more than healthy controls were also found in an earlier study[40]. However, these results were not replicated in a more recent study[26]. An examination of the frequency of worry in the different phases of BD revealed that worry was more often endorsed by individuals in their depressed phase compared to individuals in their manic phase, underlying the importance of mood state[41].

In summary, perseverative thinking has been found to be an important feature of BD, and many studies have identified its role in the severity, risk of relapse, and maintenance of BD. However, still unclear is how exactly perseverative thinking is associated with BD and whether any change in its frequency may impact the prognosis for BD. Also as yet undetermined are whether rumination and worry may differentially affect individuals with BD and whether targeting them specifically may be appropriate according to the phase of BD. More research is undoubtedly necessary to clarify if and to what degree MCT is effective in reducing perseverative thinking in BD patients. To this end, carefully designed, randomized controlled trials with sample sizes sufficient to detect clinically significant effect sizes are needed.

ATTENTIONAL BIASES (SELF-FOCUSED ATTENTION AND THREAT MONITORING)

To date, many studies have been conducted on the neurocognition of BD that have produced conflicting results due to cognitive heterogeneity and methodological differences. Factors such as different clinical and neuropsychological presentations of BD, different tools used in neuropsychological measurements, difficulties in excluding drug effects, and insufficient statistical power of sample sizes are some of the challenges to reaching consensus on the neurocognition of BD[42]. Nevertheless, more consistent results have been obtained regarding the neurocognition of BD in some domains, such as executive functions, verbal memory, and sustained attention[43].

In the literature, sustained attention is often measured with a computerized test called continuous performance test (CPT), while distinct attentional domains can be evaluated with tests like the Trail Making Test, Stroop Color-Word Association Test, and Digit Span[44]. In the CPT, a selection of stimuli is presented to the subject in an unpredictable way to focus the subject's attention. Several outcome criteria may be

obtained, such as omission error (failure to respond to the required target, which is a measure of target sensitivity), commission error (erroneous response to a non-target, which is a measure of false alarm), total number of correct responses, and reaction time[45]. Impairments have been suggested to be present in different attentional domains in particular episodes of BD[46].

In the first review regarding the attentional processes of BD patients, commission and omission errors were reported to be significantly present in manic patients and target detection (omission) errors were reported as persisting in patients with BD during remission[44]. Sustained attention deficit in BD, which is persistent in euthymia and is exacerbated in the active disorder period, has been suggested as a state-modulated deficit[47]. This finding was replicated in subsequent studies; additionally, state-dependent impairments have been proposed to be unrelated to medication, while deficits that become widespread in the acute episode may be partially related to medication[48]. Study findings have also indicated that distinguishing drug-related deficits from disease-related deficits is difficult and that drugs may have a certain degree of adverse effects on psychomotor speed and sustained attention. However, in first-episode and drug-naive patients, the cognitive deficits detected were similar to those of patients with long-term drug use[49]. This reflects the need for appropriately designed studies that can demonstrate drug effects more clearly.

Regarding attentional processes in BD subtypes, although several prior studies suggested that BD type I may be related to worse attentional performance, more recent studies uncovered that both subtypes were associated with similar attentional impairment during euthymia and that the differences between them may be related to antipsychotics, which were more likely to be used in BD type I[50]. Current meta-analyses and reviews regarding the differences between BD types I and II also suggest that the severity of attentional impairment in BD type II is similar to the severity of such impairment in BD type I[42,43,49,51]. The effect size related to attentional impairment in BD has been reported as small to medium[43,52].

Attentional bias is one of the areas that has been increasingly investigated in BD studies in recent years. In the literature, attentional bias is investigated by using tests like the dot-probe task and the affective go/no-go test and by examining attentional biases against faces and words that have affective components. In one of the earliest studies in this field, Jongen *et al*[53] found that mildly depressed patients directed their attention away from depression-related and positive words and reported this finding was mood state-dependent. They also found that the bias away from positive words could also be seen in euthymia, which may be part of a trait effect. In a study that evaluated these findings in both BD patients and their relatives, the relatives did not differ significantly from the control group in terms of attentional biases. However, mildly depressed patients exhibited attentional biases similar to those observed in the study from Jabben *et al*[54]. In another study involving people on the bipolar spectrum, the subjects were found to have a negative self-referent information processing bias that was partially mediated by depressive symptomatology[55]. On the other part of the spectrum, manic patients were found to show no attentional vigilance to happy or sad expressions, but they avoided sad expressions and focused more on happy expressions in later emotion processing[56]. Like the study by Liu *et al* [56], Gruber *et al*[57] investigated the relationship between attentional biases and hypomania proneness. Gruber and associates found that hypomania proneness was positively associated with attentional bias toward happy, but not angry or fearful, faces. These findings show distinct attentional biases may be present in both depressive and manic episodes.

These consistent results regarding attentional biases in BD, especially in depressive episodes, were confirmed in subsequent studies. However, results regarding attentional biases in euthymia were conflicting. Several studies revealed that, regardless of the episode, attentional biases were present and an increased attention to threat may be a trait-based vulnerability[58,59]. However, in a larger sampled study, no differences in attentional bias were found compared to controls in euthymia[60]. Factors such as the inability to exclude drug effects, small sample sizes, and different clinical and neuropsychological presentations of BD may have caused these inconsistent results. Taken together, attentional bias is especially apparent in the depressive episode in BD, and this effect may be state-dependent.

Recent studies also suggest the existence of biases regarding threat in BD. Increased threat sensitivity is characterized by enhanced attentional biases toward negative stimuli and away from positive stimuli and it has been viewed as enhancing the need for cognitive control[61,62]. Threat sensitivity has also been associated with depressive and anxiety disorders in the past, and recently, findings have shown that it may also

be associated with BD[63-65]. One study demonstrated that threat sensitivity is increased in those with BD, in which anxiety disorder comorbidity is up to 60%[66]. Similar findings were found in another study conducted in a pediatric BD group that revealed that children with BD and anxiety disorder comorbidity had a bias toward threat compared to those without anxiety[67]. The same study also showed that hypo/mania scores were related to a greater bias toward threatening faces, with the authors stating that "current mood state also influences threat-related attention biases" [67]. These findings, which were also present in the pediatric group, indicate that further research is required on neurodevelopmental effects on attentional biases.

A particular way of threat monitoring encountered in individuals with BD is constant mood monitoring and body scanning to determine if energy levels are somehow predictive of a new depressive episode. An early study concluded that mood monitoring implied that individuals had to be vigilant to track any changes in their mood state, which could result in repeatedly checking it but remaining confused about its nature. With an analogy to hypochondriasis, the authors suggested that the individuals' judgments about their moods could be clouded by an absorption in their mood state. Indeed, mood monitoring has been repeatedly associated with an increased self-focus, resulting in rumination and negative affectivity[68]. More recent research also demonstrated that, despite evidence to the contrary, some individuals may shift into a more depressive mood state after frequent assessment of their negative symptoms[69]. In fact, over 10% of individuals with BD reported that self-monitoring did not help to maintain their health, whereas over 25% of the participants in this survey reported that they were not sure whether self-monitoring had any effect on their health[70], confirming the earlier suggestion that repeated assessments may cloud their judgments. Such concerns were echoed in more recent surveys. Participants informed the researchers that their mood monitoring could potentially become preoccupying and unhelpful and that they might interpret their conclusions about their mood as negative when they were actually feeling well. Participants were also concerned that such practices may not seem normal and that engaging in them may draw additional attention from the general public[71]. Additionally, mood monitoring did not result in significantly decreasing mania scores[72]. Given the controversies over the effectiveness of mood monitoring in BD, experts recently published recommendations on how to implement it in routine practice. They suggested that without a clear rationale for using mood monitoring, and without reviewing the procedure with the patient, this practice can be detrimental. The experts also highlighted the need to normalize everyday mood fluctuations and to distinguish them from actual signs of relapse. The recommendations also included suggestions to respond to mood changes without mood monitoring. This set of recommendations calls for caution in employing mood monitoring in individuals with BD[73].

Studies on the attentional bias in BD have brought forward the investigation of the role of self-focused attention in BD. In past studies regarding the cognition of unipolar depression, self-focused style was found to contribute to the onset and maintenance of depression[74]. In a 3.5-year follow-up study examining the effects of self-focused attention on different stages of BD, controlling for depressive and manic symptoms, bipolar patients were found to experience significantly higher levels of depressive rumination and private self-consciousness than the controls[75]. These findings seem consistent with the findings from Johnson *et al*[33] that patients with BD have a ruminative response pattern to both depressive and positive moods. Self-focused attention research seems to mostly be conducted with anxiety and depression; thus, further studies regarding the relationship between self-focused attention and BD are needed.

In terms of cognitive self-consciousness, previous research demonstrated that patients with BD reflected more frequently on themselves than patients with schizophrenia, but they did so at rates similar to those of healthy subjects. Further, focusing on the self negatively correlated with excitement and hostility[76]. The researchers of another study, comparing individuals with BD and schizophrenia, arrived at the same conclusion, indicating that self-reflection was higher in the BD group[77]. Conversely, these findings were not demonstrated in a more recent study in which individuals with BD failed to discriminate not only from individuals with schizophrenia but also from healthy controls[78]. A similar non-significant difference was reported in individuals with BD subtypes and healthy controls[26]. Cognitive self-consciousness was found to be higher in patients with BD compared to controls, and it also correlated with an earlier age of onset of an affective disorder and with the severity of depression. The severity of depressive symptomatology was the only predictor of self-focused attention, highlighting the possibility of the specific role of depressive episodes in cognitive self-consciousness[79]. However, other studies have not

replicated this finding; instead, they reported that self-focused attention may more specifically correlate with anxiety levels. Interestingly, the previous study also did not find any significant differences between individuals with unipolar or bipolar depression and healthy controls[80]. This result was obtained in a later study as well [28]. However, another study claimed that, although individuals with unipolar and bipolar depression did not differ from each other on a measure of self-focused attention, both scored higher than healthy controls. This study also reported that cognitive self-consciousness correlated weakly with both manic and depressive symptom severity[81]. On the other hand, another study showed that individuals with BD did not differ from healthy controls on cognitive self-consciousness, but cognitive self-consciousness significantly correlated with worsening in executive functioning, according to the researchers[82]. Further, a comparative study identified that the need to control thoughts was associated with thought disturbance, whereas this was not valid for individuals with schizophrenia[78]. Focusing particularly on suicide attempts in BD patients, another study reported that self-focused attention may be protective against suicide attempts. The authors suggested that being aware of one's own thoughts may alert the individual about any threatening suicidal ideations, which may prompt the individual to seek help. In this study, cognitive self-consciousness was significantly lower in the group of individuals who previously attempted suicide[83]. Given that this is a rather controversial finding and interpretation of the metacognitive model, we strongly urge waiting for further studies to confirm this finding.

In summary, the literature data on attentional biases illustrate the following: deficits in attentional processes in the euthymic period in BD, the presence of mostly commission errors, that these impairments can also be seen in people with genetic risk for BD, and that attentional impairments are widespread in patients with mania. Although not consistent, in euthymia and in relatives of patients with BD, the literature shows that state-dependent, mood-changing attentional biases and a ruminative self-focused attention are present. Studies on cognitive bias modification demonstrate that attentional biases that are present in depression may be modified and that this may lead to changes in mood and reactivity to stressful events[84,85]. In BD patients, reducing the severity of symptoms and the risk of relapse may be possible with metacognitive interventions regarding self-focused attention and attention biases.

DYSFUNCTIONAL (BACKFIRING) COPING STRATEGIES

Patients diagnosed with BD need to cope with the various problems they encounter, the outcomes of their mental disorder, and unpleasant situations in general to stay healthy[86]. Coping has various definitions. Lazarus defined coping as both thoughts and behaviors that individuals use to control the internal and external requirements of conditions that are perceived as stressful[87]. Compas *et al*[88] described coping as a self-regulatory process volitionally and purposely explicitly established in response to stress. Considering the executive dysfunction due to neurotoxicity in BD, coping abilities have been reported to play a key role in modulating the relationship between stress and episodic recurrence[89]. It was reported by Goossens *et al*[86] that, among those with euthymic BD, those who had had 10 or more acute depressive episodes throughout their lives chose a more passive coping style. In addition, outpatients with BD had a less active reaction pattern and a more avoidant coping style compared with healthy people[86].

Green *et al*[90] compared the use of certain cognitive strategies for regulating negative emotions in patients with BD type I, unaffected relatives of BD patients, and healthy controls. The results were interesting: The BD group reported more frequently using maladaptive regulatory strategies, such as rumination, catastrophizing, and self-blame, which were previously associated with depression[90]. In a paper describing another study, Paans *et al*[91] reported that better executive functioning and fewer depressive symptoms were associated with more active coping in older adults with BD. In addition, they noted that associations between executive functioning and coping styles became non-significant when the depressive symptoms in euthymic participants were considered, indicating that even subclinical depressive symptoms may negatively influence active coping[91].

Fletcher *et al*[92] aimed to address the cognitive and coping styles in patients diagnosed with BD types I or II. They indicated positive relationships existed between both BD subtypes and depressive severity and maladaptive coping styles. Furthermore, a wider variety of negative cognitive styles were associated with BD type II depression symptoms[92]. An editorial by Grunze[93] underlined the results of the

study by Fletcher *et al*[92] and stated that only low levels of seeking support to cope with stress as a coping style, which increased the likelihood of a depressive episode at follow-up, predicted BD type I depression. Grunze[93] suggested that subtype-specific identification of cognitive and coping styles may identify and quantify the risk of relapse, which may provide clinicians with a way to reduce the risk of relapse by modifying specific areas of negative cognition and maladaptive coping styles.

Pavlickova *et al*[36] reported that adaptive coping significantly predicted an increase in self-esteem, which was associated with a decrease in ruminative thinking in a specified period. Similarly, Leung *et al*[94] showed that the level of adaptive coping predicted an increase in positive affect in patients with BD.

Another study examining BD aimed to calculate the cumulative effect of childhood abuse, neuroticism, social support, and coping style on depressive symptoms. The results showed that emotional childhood abuse, neuroticism, social support use, and active coping style affected depressive symptoms and indicated that 45.6% variability in depressive symptoms could be explained by these factors[95].

Suh *et al*[96] recently studied the similarities and differences in coping styles between BD and depressive disorder patients. More avoidant and task-oriented coping was associated with individuals with BD independent of the effect of depressive symptoms. The results revealed significant negative correlations between the severity of depression and both task and avoidance-oriented coping styles in both the BD group and the depressive group. However, avoidance-related coping had a significant negative correlation with depression scores only in the BD group.

Individuals with BD tended to believe that they needed to control their thoughts more frequently than healthy controls [34,82], which was evident for both BD subtypes [26,28]. The need to control thoughts seemed to negatively affect neurocognitive functioning[82]; furthermore, individuals with BD who had previously attempted suicide scored higher than those who had never attempted suicide, suggesting that the need to control thoughts was associated with increased risk for suicide attempts[83]. Additionally, thought control strategies were associated with an earlier age of onset of an affective disorder and with the severity of a depressive episode. Individuals with BD used worry and self-punishment more frequently than the control subjects as thought control strategies, whereas they used distraction and social control less frequently than the controls[34]. However, patients with BD in a depressive episode did not differ significantly from patients with unipolar depression in the frequency of their need to control thoughts, but the need to control thoughts did positively correlate with depression severity[80,81].

In summary, maladaptive coping strategies were frequently reported in patients with BD. These strategies are found to be associated with depression severity, negative affect, and relapse risk. Metacognitive interventions that aim to change these maladaptive coping strategies may improve both disorder severity and relevant BD aspects.

DYSFUNCTIONAL (MALADAPTIVE) METACOGNITIVE BELIEFS IN BD

Dysfunctional metacognitive beliefs are known to be transdiagnostic processes. A previously published meta-analysis included participants with BD. This meta-analysis concluded that negative metacognitive beliefs (beliefs about the uncontrollability and dangerousness of thoughts), lack of cognitive confidence, heightened cognitive self-consciousness, and the need to control thoughts were more prevalent in various psychiatric disorders. The authors also suggested that although metacognitive beliefs were transdiagnostic, specificity of higher dysfunctional metacognitive beliefs was also found in different diagnostic categories[97].

Studies specifically focusing on dysfunctional metacognitive beliefs in BD individuals have recently gained interest among researchers. Compared to healthy controls, individuals with BD reported higher scores for negative metacognitive beliefs, lack of cognitive confidence, and the need to control thoughts[26,80,82]. Other studies also suggested that higher self-consciousness was evident in individuals with BD[34,81]. Contradicting previous results, Favaretto *et al*[26] further claimed that positive metacognitive beliefs were more frequently endorsed by individuals with BD type II than by healthy controls. Other research has also pointed out that fewer metacognitive deficits may be present in those with BD than in those with schizophrenia[76-78]. Additionally, other researchers indicated that metacognitive beliefs may mediate the effect of early emotional abuse on psychotic symptoms through an affective pathway[98]. Dysfunctional metacognitive beliefs were more strongly

associated with depressive symptomatology[82] and with suicide attempts in individuals with BD type I[83]. In a study that compared healthy controls with individuals with both BD subtypes and with major depressive disorder on their metacognitive beliefs, the diagnostic groups did not differ significantly from each other, but they scored higher than the control group on negative metacognitive beliefs, lack of cognitive confidence, and the need to control thoughts. However, the diagnostic groups did not separate from the healthy controls on positive metacognitive beliefs and cognitive self-consciousness. This study also investigated metacognitive beliefs about rumination of the participants. The results revealed that, while negative beliefs about rumination (uncontrollability, danger, and negative interpersonal and social consequences) were higher in the diagnostic groups, scores on the positive beliefs about rumination did not differ between the groups[28]. In addition, preliminary results demonstrated that metacognitive interventions may be useful for individuals with BD[15,76,99].

In summary, although individuals with BD are known to present with dysfunctional metacognitive beliefs, further studies are still needed to clarify how these beliefs are associated with depressive symptomatology and whether they may also have an impact on hypomanic/manic symptomatology. Further studies focusing specifically on BD subtypes and different phases of the disorder are also needed. Assessment instruments developed for individuals for BD are also lacking. The effectiveness of MCT in BD needs to be investigated in large-scale, randomized controlled studies.

PROPOSED THEORETICAL FRAMEWORK FOR MCT IN BD

As summarized in the previous sections, components of CAS and dysfunctional metacognitive beliefs are evident in BD. Despite the minimal research on the effectiveness of MCT for BD, acknowledging the transdiagnostic nature of MCT, a theoretical framework for applying MCT for BD patients may be proposed. Following the treatment steps of the only published study on applying MCT in BD[15], which was based on the generic structure of MCT[12], we propose a sequential treatment protocol for BD (Figure 1): (1) Case conceptualization; (2) Socialization to the model and treatment; (3) Shifting the patient to the metacognitive mode and increasing meta-awareness of perseverative thinking; (4) Implementing the attention training technique (ATT); (5) Practicing detached mindfulness (DM); (6) Postponing perseverative thinking; (7) Modifying the uncontrollability of perseverative thinking beliefs and challenging other negative metacognitive beliefs; (8) Exploring and abandoning dysfunctional coping strategies, including all kinds of threat monitoring strategies, and suggesting behavioral activation; (9) Challenging positive beliefs about perseverative thinking; (10) Identifying and modifying negative beliefs about mood states; (11) Working on a relapse prevention plan with the patient; (12) Targeting fears of recurrence; and (13) Scheduling booster sessions.

This proposed treatment protocol is mainly based on the MCT treatment plan for depressive disorders[12]. However, for the plan to be compatible with the needs of individuals with BD, the therapist must make some adjustments and modifications. For the metacognitive case conceptualization of the patient, the therapist may need to focus on positive trigger thoughts (or other positive internal experiences), as well as negative ones. To identify the perseverative thinking style of the patient, the therapist may need to make note of any responses to positive affect and worries in addition to depressive rumination. The negative consequences section of the case conceptualization diagram needs to be completed with consideration of any increase in self-reported energy levels, hypomanic/manic affective tendencies, hyperactivity, increased goal-directed activities, changes in sexual interest, impulsivity, increased self-esteem, and grandiosity, in addition to conventional thoughts, affect, and behaviors observed in depression. The therapist and patient must work collaboratively to identify ruminative thinking styles and worrying, with a special focus on positive rumination and how that may interfere with the patient's goal to stay in remission. The role of positive rumination on unwanted consequences should be explored, and postponement and/or abandonment of positive rumination must be encouraged, as it is for depressive rumination and worrying. The uncontrollability and dangerousness of all types of perseverative thinking styles need to be challenged. Modifying beliefs about the negative interpersonal consequences of perseverative thinking need to incorporate a discussion on the responses to positive affect in addition to the conventional discussion about depressive rumination and worrying. Any beliefs about the advantages of perseverative thinking need to be questioned, specifically questioning

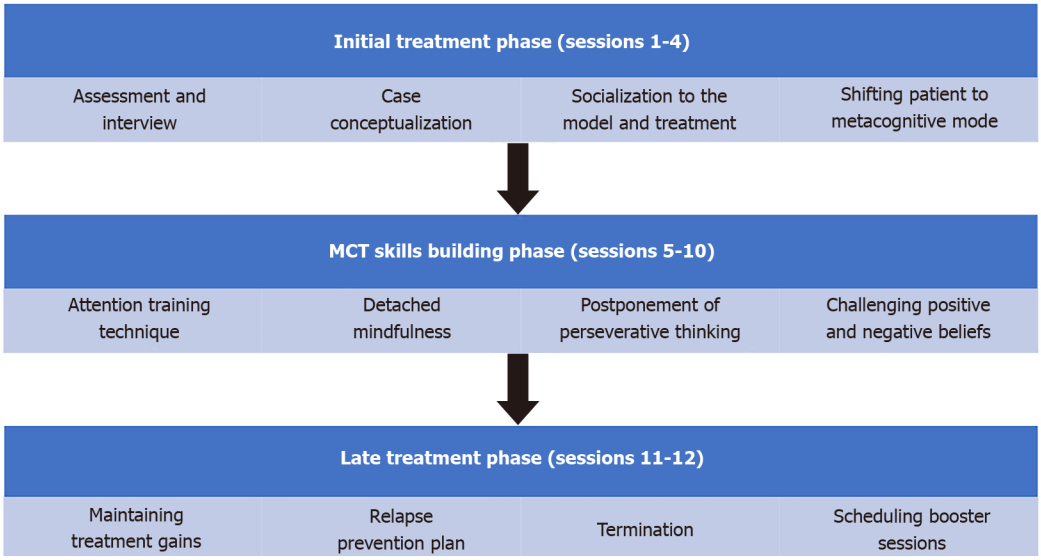


Figure 1 Structure of the proposed metacognitive treatment protocol for bipolar disorder. MCT: Metacognitive therapy.

the perceived positive effects of positive rumination along with the conventional work on depressive rumination and worrying. Dysfunctional coping strategies involving thought control strategies, inactivity, self-harm, alcohol/substance use, emotional avoidance, social withdrawal, and so on may be targeted as they are with a patient with depressive disorder. For the BD patient, the therapist also must acknowledge the possibility of increased goal-directed activity, hyperactivity, staying up all night to keep up with high expectations of self, impulsive behaviors, and related behaviors. Additionally, self-focused attention and constantly monitoring energy levels and mood states may be problematic for the patient. Since a recurrence may be feared and warning signs for new episodes may be in focus, the patient may wake up every day with an initial body scanning for any signs and symptoms suggestive of a new mood episode. The patient needs to abandon such biased and backfiring threat monitoring strategies. Although this is discussed with patients with depressive disorder, the therapist may also spend some time with BD patients focusing on the effects of incessantly looking for possible early warning signs and how this strategy may interfere with the patient's interpretation of naturally occurring mood swings. Other MCT techniques, such as ATT, DM, relapse prevention strategies, and setting up booster sessions, may follow the guidelines for patients with depressive disorders with modifications for patients with BD where necessary.

CONCLUSION

In conclusion, the metacognitive model of BD may provide a new perspective to further understand the underlying psychological mechanisms in patients with BD. Therefore, for a subgroup of patients with BD who fail to respond to evidence-based psychopharmacological and adjunctive psychotherapeutic interventions, MCT may be an alternative treatment option. More randomized controlled research undertaken in large samples is necessary to present more evidence on the effectiveness of MCT in BD.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 September 19; 11(9): 605-618

DOI: 10.5498/wjp.v11.i9.605

ISSN 2220-3206 (online)

MINIREVIEWS

Gastrointestinal disease in children with autism spectrum disorders: Etiology or consequence?

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Author contributions: Krigsman A and Walker SJ contributed equally to this work; both authors have read and approve the final manuscript.

Conflict-of-interest statement: No conflicts-of-interest to report.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United States

Peer-review report's scientific quality classification

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Abstract

Chronic gastrointestinal (GI) symptoms and disorders are common in children with autism spectrum disorder and have been shown to be significantly correlated with the degree of behavioral and cognitive impairment. In this unique population, GI symptoms often arise very early in development, during infancy or toddlerhood, and may be misdiagnosed - or not diagnosed at all – due in part to the challenges associated with recognition of symptoms in a minimally or non-communicative child. Evidence demonstrating that the gut-brain-axis can communicate gut dysbiosis and systemic immune dysregulation in a bidirectional manner raises the question as to whether an untreated gastrointestinal disorder can directly impact neurodevelopment or, conversely, whether having a neurodevelopmental disorder predisposes a child to chronic GI issues. From the data presented in this mini review, we conclude that the preponderance of available evidence would suggest the former scenario is more strongly supported.

Key Words: Autism spectrum disorder; Gastrointestinal disease; Immune dysregulation; Neurodevelopment

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Core Tip: Children with autism spectrum disorder are at a significantly increased risk for chronic gastrointestinal issues from an early age. Clinicians and caregivers should be made aware of this association and provided with the tools necessary for recognition of gastrointestinal (GI) symptoms in these children. Because the first several years is a critical developmental window in the life of a child, and because of the demonstrated

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: June 2, 2021
Peer-review started: June 2, 2021
First decision: June 23, 2021
Revised: June 24, 2021
Accepted: August 12, 2021
Article in press: August 12, 2021
Published online: September 19, 2021

P-Reviewer: Saad K, Siniscalco D
S-Editor: Yan JP
L-Editor: A
P-Editor: Guo X



correlation between GI symptom severity and severity of autism spectrum disorder behaviors and cognition, it is plausible that a neurodevelopmental diagnosis may result from an untreated, persistent state of GI/immune dysregulation.

Citation: Krigsman A, Walker SJ. Gastrointestinal disease in children with autism spectrum disorders: Etiology or consequence? *World J Psychiatr* 2021; 11(9): 605-618
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/605.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.605

INTRODUCTION

Children with autism spectrum disorder (ASD) display gastrointestinal (GI) signs (*i.e.*, abnormalities noted by an observer) more frequently than their neurotypical counterparts[1]. These signs may present as constipation, diarrhea, abdominal pain, vomiting, food refusal, gastroesophageal reflux, malodorous macroscopic malabsorption, failure to thrive, or weight loss and although nearly all children experience gastrointestinal issues at some point during childhood, the reasons for this increased prevalence of GI signs in children with ASD has not been clearly established. This raises the question as to whether autism renders children more vulnerable to chronic GI issues, or whether chronic GI issues, especially in infancy and early childhood, increases the risk for developmental delay and/or ASD.

Verbally (or non-verbally) communicative children with ASD who can express what they are feeling are known to experience GI symptoms (the self-expressed feeling of an abnormality such as pain) at a greater frequency than their neurotypical counterparts, whereas children with ASD who have an underlying GI disorder, but who are unable to express what they are feeling, are known to manifest GI symptoms as extremes of behaviors, such as aggression, self-injury, and excessive self-repetitive behaviors[2]. It is this group of (treatable) children that is most at risk for not receiving a GI diagnosis and not receiving the proper clinical care.

Finally, core ASD features are more pronounced in GI symptomatic children with ASD, and the severity of GI signs and symptoms have been shown correlate with the severity of ASD features[3]. The constellation of GI sign/symptom presentations in ASD, as well as the GI-behavioral association, has been reviewed elsewhere[4] and will not be the focus of this review. It is worth noting here, however, that the frequent anecdotal reports of improvement (from modest to remarkable) in core ASD features following successful treatment of an underlying GI disorder provides compelling evidence that the two are interrelated.

In this mini review, the fundamental conundrum we wish to explore is: (1) Does chronic gastrointestinal dysfunction, especially at a very young age, predispose a child to developmental delay or disorder (etiology); or (2) Does having a developmental delay or disorder increases the risk of gastrointestinal dysfunction in children (consequence).

IMPORTANCE TO THE MENTAL HEALTH PROFESSIONAL

The relevance and importance of this information to the mental health professional cannot be overstated. Although it is clear that all core ASD features or their extremes cannot be explained solely by an underlying GI pathology, the documented relationship between these two demands vigilance on the part of those who interact with and care for the child with ASD. If a caregiver or medical professional suspects and/or is made aware that GI signs/symptoms exist, then appropriate pediatric gastroenterology referral is warranted. The logical consequence of acknowledging this relationship between GI signs/symptoms and ASD behaviors (documented[5], though not yet formally addressed in most of the medical literature) is that it will allow for accurate identification and treatment of GI pathology to commence and, when treatment is successful, will ultimately decrease the unfortunate dependence on often unnecessary behavior modifying medications and their associated adverse effect profiles. Most importantly, this strategy directly targets the underlying pathology as opposed to simply modifying the resultant disease related behaviors.

HOW DOES GASTROINTESTINAL DYSFUNCTION INFLUENCE BEHAVIOR IN AUTISM SPECTRUM DISORDER?

The vast autism-GI literature provides an additional layer of fundamental mechanistic questions regarding the notion that central nervous system (CNS) pathology alone is responsible for ASD behaviors. If GI signs/symptoms correlate with the degree of ASD features in children with ASD, and if they are in some cases the sole presenting indication of an underlying cognitive/behavioral disorder, what might the mechanism be? Although it is tempting to attribute behaviors as directly resulting from unattended pain (an"acting out"of sorts), abundant anecdotal experience with communicative children with ASD reveals that they experience intense compulsions, thoughts, and feelings during active GI symptoms, even in the absence of pain. This question of an underlying mechanism to explain how GI dysfunction can impact ASD behaviors has led to speculation that a "gut-brain-axis", in which the products of one or more pathological GI processes contributes to CNS dysfunction, is the nexus.

The obligatory first step then in answering this pathophysiologic question lies in the clinical approach taken by the gastroenterologist when confronted with these signs/symptoms in the child with ASD. The standard of care for these children is to address their GI signs/symptoms in identical fashion as one would the child who is neurotypical, while at the same time being mindful of the unique behaviors that may be the only sign of underlying GI pathology. GI evaluation is therefore sign/symptom driven, and when standard non-invasive diagnostic tests (blood, stool, urine, imaging studies) are unrevealing, empiric finite trials of medication (*e.g.*, H2 blockers, laxatives, *etc.*) may be warranted. If unsuccessful, the standard of care at that point is usually endoscopy with biopsy.

The most important clues as to the mechanism of the unidirectional GI-CNS linkage (beyond the simple behavioral response to pain) would be expected to lie within the GI mucosa, and in our experience treating > 1500 GI-symptomatic children with ASD, the most common pathologic finding at endoscopy in such cases is non-specific inflammation. Therefore, the putative mechanism that will be described in the following sections differs from existing mechanistic hypotheses that have been put forth thus far in the literature in that it is based solely on human GI mucosal pathology, identified specifically (and often uniquely) in children with ASD, that has been published over the past twenty years. A mechanistic theory will then be proposed that incorporates these findings into the published systemic and CNS pathology of ASD.

GASTROINTESTINAL INFLAMMATION IN AUTISM SPECTRUM DISORDER

Kanner[6]'s seminal paper that describes 11 children with autism mentions the finding of GI disturbances in many of them, but it was not until more than 50 years later, in 1998, that the first histologic evaluation and description of GI inflammation of GI symptomatic children with ASD was published. The ongoing and evolving story of ASD related GI inflammation might appear to be better suited for a gastroenterology journal, however since GI disease is being evaluated in the context of ASD, journals focused on autism or psychiatry (ASD is diagnosed as a psychiatric illness, after all) are equally well suited. Regardless of the venue, the story itself is illuminating in so many respects that academic fidelity dictates that if we are to provide meaningful context, any discussion of this topic must necessarily include the chronologic appearances in the literature of evidence of gastrointestinal inflammation.

In 1998, led by world renowned pediatric gastroenterologist John Walker-Smith, the inflammatory bowel disease (IBD) study group at the Royal Free Hospital in London published a case report in the lancet about 12 children with regressive pervasive developmental disorder, characteristic of autism, who underwent diagnostic endoscopy for evaluation of chronic GI symptoms including diarrhea, abdominal pain, abdominal distention, and food intolerance[7]. Chronic colitis (the excessive presence of lymphocytes - primarily plasma cells - in the lamina propria) was found in 11 of the12 children, and active colitis (neutrophilic infiltration of the epithelium and lamina propria) was found in 5. Intraepithelial lymphocytosis of the cecum was observed in 1 patient. Importantly, and unlike the "classic" inflammatory bowel diseases Crohn's disease (CD) and ulcerative colitis (UC), the chronic inflammatory changes in these children were present in areas of the colon that appeared endoscopically normal. The publication of this case series created a media frenzy at the time because of questions it raised regarding pediatric vaccination safety, ultimately prompting a "retraction of an interpretation" six years later in 2004[8]. Full retraction of the paper by the lancet

occurred in 2010 following a four-year investigation of the paper's findings by England's General Medical Council (GMC), a body that concluded patients were not in fact consecutively referred and that the Institutional Review Board authorization was not appropriately obtained. But, as will be described next, by the time the GMC findings had been rendered, the histologic findings had already been replicated and expanded upon by these and other investigators, at other institutions, and using additional methodologies.

The following year, in 1999, Horvath *et al*[9] published a clinical report describing the histologic (but not endoscopic) findings in 36 children with ASD and GI symptoms of diarrhea, flatulence, nighttime awakening, unexplained irritability, and abdominal distention. In that study it was found that 25 (69.4%) of the children had histologic gastroesophageal reflux, almost all of whom had unexplained irritability as a key symptom. Additionally, Paneth cell hyperplasia, a measure of increased crypt mitotic activity secondary to inflammatory mucosal damage, was significantly increased. The authors do not discuss therapeutic interventions.

Before proceeding further through this brief review of the ASD-GI inflammation literature, it is important to note that not all "inflammation" is equal. For example, the cellular infiltrate of acid related disease is composed of different cellular lineages and intensities than, for example, CD. Even within the classification of classic IBD (CD and UC), the types of inflammatory cells differ between the differing IBD diagnoses. Using tissue immunostaining, Furlano *et al*[10] demonstrated not only a significant non-specific lymphocytic inflammatory plasma cell, CD3, and CD8 T-cell elevation in the colon of GI symptomatic children with ASD compared to healthy controls, but that there was also an excess γδ-T-cell presence that distinguishes autistic colitis from classic IBD.

Attention then turned to the upper gastrointestinal tract where, in 2002, the use of immunohistochemical staining again showed the non-specific increased CD3 and CD8 T-cell inflammatory infiltrate in the mucosa with the additional finding of a thickened basement membrane, a feature often found in the intestine of patients with systemic autoimmune disease such as diabetes, rheumatoid arthritis, and gluten sensitive enteropathy (celiac disease)[11]. However, what distinguished the duodenal inflammation from all previously reported forms of childhood enteropathy was the presence of a unique feature of autoimmunity, namely the presence of IgG colocalizing with complement c1q on the basolateral enterocyte membrane.

Next, in 2003, Ashwood *et al*[12] reproduced the findings of Furlano and Torrente using the newer technique of flow cytometry (as opposed to immunostaining). This group demonstrated elevated CD3 and CD8 cellular infiltrate in the mucosa (duodenum, terminal ileum, and colon) of 52 GI symptomatic children with ASD when compared to inflamed and non-inflamed mucosal tissues from 54 non ASD controls. They also reported statistically similar degrees of infiltrate compared to inflamed controls having other diagnoses (*e.g.*, IBD, indeterminate colitis, food allergy, celiac disease, *etc.*). Additionally, intraepithelial lymphocytosis and B-cell infiltration were present in GI symptomatic children with ASD but not in healthy children. The authors noted that this study confirmed and expanded upon the previously described unique nature of the combined inflammatory components in GI symptomatic children with ASD. Importantly, it was the first time that this pathology was shown to exist simultaneously in the small and large intestine.

In 2004, Torrente *et al*[13] described unique inflammatory pathology in the stomach of 20 (out of 25; 80%) GI symptomatic children with ASD when compared to 30 non-ASD controls. This pathology profile, like the one described by Torrente in the small bowel, was unique and unlike the focal enhanced gastritis seen in CD. Specifically, it consisted of a markedly elevated CD8 T-cell infiltration, marked presence of intraepithelial lymphocytes, and had the same subepithelial basement membrane IgG deposition colocalization with complement c1q seen in the small bowel.

In 2005, Balzola *et al*[14] reported similar chronic active colitis and gastritis (with gastric pseudopolyps) in a 28-year-old patient with regressive autism. Importantly, capsule endoscopy was also performed and revealed jejunal and ileal erosions and ulcerations. This remains the only published report of capsule endoscopic findings in a patient with autism. The authors suggested that their findings of small bowel disease beyond the limits of the duodenum and terminal ileum "demonstrate the potential for involvement of the entire bowel in this inflammatory disease".

A 2008 case report of two GI-symptomatic patients (one 18-year-old male; one 19-year-old female) with autism describes the precise histopathologic findings previously reported [*i.e.*, non-specific gastritis, focal active colitis, and lymphonodular hyperplasia (LNH) of the terminal ileum] and reported clinical GI symptom improvement in the male patient following a course of steroids after a failed trial of high dose 5-ASA[15].

In their discussion of the findings, the authors commented that "although the idea of a shared pathophysiology between GI disease and autism remains controversial, the evidence presented so far warrants further exploration at the very least" and they advocated for a heightened awareness and lower threshold for work-up and management on this population.

In 2010, Krigsman *et al*[16] reported on the retrospective histologic findings (on routine H&E staining) as reported by the hospital pathologists, of 143 consecutive children with ASD and chronic GI symptoms. It remains the largest study of GI symptomatic ASD mucosal biopsy tissue to date. Based on H&E staining, the authors found ileitis in one third (35%), and ileal or colonic chronic active inflammation in nearly three fourths (74%) of the children. LNH, a feature of inflammation that may be observed at any site while not by itself meeting the definition for inflammation, was present in nearly three fourths (73.2%) of the patients, and for this patient series the presence of LNH predicted the presence of inflammation. Regarding LNH in general, and specifically in children with ASD, this finding represented an important observation because although the prominent presence of LNH in GI-symptomatic children with ASD had been noted (and vigorously debated) in the literature, this case series, due to the large size of the cohort, was the first to report a statistically significant link between LNH and actual mucosal inflammation. Regressive or plateau autism was more strongly linked to ileocolitis than early onset autism. This case series did not seek to identify inflammatory characteristics unique to ASD.

In 2013, Walker *et al*[17] expanded upon the uniqueness of the ASD-associated enterocolitis with characterization of the infiltrates at the molecular level. This case-control study utilized mRNA transcriptome profiling of inflamed ileal and colonic tissue from GI-symptomatic children with ASD and from controls consisting of anatomically matched (ileal and colonic) GI biopsy tissues from GI-symptomatic non-ASD control patients with either: (1) No histologic evidence of pathology; (2) CD; or (3) Ulcerative colitis. Comparison of differentially expressed transcripts between the ASD samples and each of the non-ASD groups showed a clear distinction between the ASD-inflamed mucosa and all other groups. Of particular interest, while there was some degree of overlap between gene expression in inflamed tissue from GI-symptomatic children with ASD and the control samples from non-ASD children with IBD (both CD and UC), no significant overlap existed between ASD and non-diseased controls. The authors noted that this correlates well with the similarities of GI symptom expression and response to therapy as seen in their clinical experience with these patients. Nearly identical molecular profile patterns emerged from both the ileal and colonic mucosal specimens from GI-symptomatic children with ASD which served to confirm the notion of unique ASD inflammatory patterns in both the small and large intestine. The differentially expressed mucosal transcripts unique to ASD that were identified in this study were subsequently evaluated in a follow up 2016 study that compared mucosal gene expression to blood gene expression simultaneously obtained in the same patients, to identify which of these biomarkers might serve as a molecular signature (*i.e.*, a "blood test") for the presence of ASD-specific inflammatory bowel disease[18].

A subsequent 2016 report by Kushak *et al*[19] evaluated intestinal function in GI-symptomatic children with autism by measuring duodenal disaccharidase activity (lactase, sucrase, and palmitase), intestinal permeability (endoscopic infusion of rhamnose and lactulose followed by measurements in urine over the next 5 h), and fecal markers of intestinal inflammation (stool calprotectin). Results suggested that intestinal permeability, brush border enzyme activity, and the frequency of inflammation did not differ between children with or without autism. Routine H&E staining showed no significant difference in the frequency of gastric or intestinal inflammation between GI symptomatic ASD and non-ASD children and although 52% of children in the ASD group had some inflammation in the gastrointestinal tract, "it was generally mild and nondiagnostic". The authors concluded that children with autism who have symptoms of GI disorders exhibit objective findings that are similar to those in children without autism.

Lastly, Alessandria *et al*[20] investigated the distribution of human leukocyte antigen-DQ2/DQ8 typing in GI-symptomatic patients with ASD, together with its correlation with duodenal histology and response to a gluten free casein-free diet. The study found unexplained duodenal intraepithelial lymphocytosis in 37% (56/151) of GI symptomatic ASD children, none of which were found to have celiac disease serologic markers. The authors concluded that their results suggest that GI-symptomatic children with ASD seem to have a high prevalence of duodenal histologic inflammation that is not linked to celiac disease.

INTESTINAL MUCOSAL PRO-INFLAMMATORY CYTOKINE ACTIVITY IN AUTISM SPECTRUM DISORDER

Evaluation and comparison of biopsy obtained mucosal tissue from the terminal ileum, ascending, and descending colon from GI-symptomatic children with pervasive developmental disorder (PDD) with age matched controls was first reported in 2003 by DeFelice *et al*[21]. Study subjects consisted of 6 children with PDD (3 with a specific diagnosis of autism or ASD) and 9 neurotypical controls. Using an ELISA kit assay of organ culture supernatants, the authors found no statistically significant differences in the concentration of IL-6, IL-8, and IL-1β between PDD and controls. Histologic findings for all patients, based on H&E staining, were nonpathological. The authors concluded that the data failed to support an association between autism and GI inflammation.

In 2004, Ashwood *et al*[22] prospectively tested the hypothesis that GI-symptomatic children with ASD demonstrated increased numbers of pro-inflammatory cytokine producing CD3+ lymphocytes. As compared to the previously cited 2003 study, this prospective and larger study of 21 children with ASD and 65 neurotypical pediatric controls focused on the intracellular content of pro-inflammatory cytokines as opposed to the cellular supernatant and evaluated the number of pro-inflammatory cytokine containing CD3+ lymphocytes using multicolor flow cytometry. Significant findings included elevated pro-inflammatory cytokine containing lymphocyte counts in children with ASD *vs* controls, particularly lymphocytes containing TNF-α, IL-2, IL-4, and IFN-γ. Significantly, the counterregulatory IL-10 was reduced in ASD as compared to controls. These trends were found in both the duodenum and colon, as well as in both the epithelium and lamina propria. The authors concluded that that there is a consistent profile of CD3+ lymphocyte cytokines in the small and large intestinal mucosa of GI-symptomatic children with ASD, providing further evidence of a diffuse mucosal immunopathology that may respond to dietary and immunomodulatory therapeutic approaches.

In 2006 Ashwood *et al*[23] using a different prospective patient cohort consisting of GI-symptomatic children with ASD (n = 18), and typically developing controls (n = 27), including non-inflamed controls (NIC), and inflamed GI control children with CD, further elaborated on their 2004 findings. As in the earlier study, the group used flow cytometry to assess the CD3+ lymphocyte intracellular pro-inflammatory and counter-regulatory cytokine profiles, this time in mucosal tissue from the terminal ileum. In this study, the CD3+ lymphocyte cytokine profiles were also measured in peripheral blood and correlated to those from the mucosa. In both the peripheral blood and mucosa, CD3+ TNFα+ and CD3+ IFNγ+ were increased in children with ASD compared to NIC, reaching levels similar to those seen in CD. In contrast, peripheral and mucosal counterregulatory CD3+ IL-10+ were markedly lower in GI-symptomatic children with ASD compared to NIC and CD controls. The authors concluded that there was a unique pattern of peripheral blood and mucosal CD3+ lymphocyte intracellular cytokines, consistent with significant immune dysregulation, in that ASD cohort. This 2006 paper marks the last published investigation of mucosal inflammatory cytokine findings in children with ASD and chronic gastrointestinal disease.

In the years between 2006 and 2018, as the incidence of autism continued to rise (according to official reporting from the CDC) and the interest in identifying biomarkers for ASD was high, there was a renewed focus (and a concomitant rise in peer-reviewed publication activity) on peripheral cytokine activity in children with autism. A 2019 meta-analysis on all circulating (blood, serum, or plasma) pro-inflammatory cytokine related literature in ASD identified 38 studies, with a total of 2487 participants (1393 with ASD and 1094 non-ASD controls) and found evidence for higher concentrations of IFN-γ, IL-1β, IL-6 and TNF-α in participants with autism[24]. A second meta-analysis by the same group, also published in 2019, examined levels of circulating anti-inflammatory cytokines in ASD[25]. This report summarized data from 25 studies with a total of 1754 participants (1022 patients with ASD and 732 controls) and found lower concentrations of IL-10 and IL-1Ra in ASD subjects compared to controls.

MUCOSAL BRUSH BORDER DIGESTIVE ENZYMES

Disaccharidases, the enzymes that break down dietary carbohydrates, reside in the brush border lining of the small bowel. Deficiencies in the level of these enzymes and/or their activity can lead to unabsorbed carbohydrates reaching the colon where

they are fermented by colonic bacteria. Aside from causing symptoms of diarrhea and gaseousness, these fermentation products have been hypothesized to play a role in exacerbating behavioral symptoms in children with ASD, possibly through abnormal absorption in the permeable GI mucosa. Due to the accessibility of the duodenum *via* endoscopic biopsy, the levels and activity of these enzymes in the mucosa can be measured relatively easily and as a result, several studies have been able to explore disaccharidase activity deficiencies in children with ASD.

For example, in 1999, Horvath *et al*[9] evaluated the structure and function of the upper GI tract in a group of 36 GI-symptomatic children with autism and found that 58% (21/36) had deficiencies in at least one brush border disaccharidase enzyme, most often lactase (14/21). Kushak *et al*[26] measured disaccharidase activity in duodenal biopsies from 199 GI-symptomatic individuals with autism and reported a lactase deficiency in 58% of autistic children < 5 years old and 65% in older patients. Finally, Williams *et al*[27] in a small case control study that investigated impaired carbohydrate digestion and transport in the GI tract of children with autism and GI disease compared to controls (GI disease alone), found deficient ileal mRNA transcripts encoding intestinal disaccharidases and hexose transporters in the children with ASD. This approach, though novel, did not ultimately measure actual enzyme activity, but the finding of deficient transcript levels provided additional support for the findings reported by Horvath *et al*[9] and Kushak *et al*[19].

Of interest is the case-control 2016 study by Kushak *et al*[19] which again found a similarly high frequency of lactase and other brush border enzyme deficiencies in GI symptomatic children with ASD, but also a similarly high frequency of disaccharidase deficiency in GI symptomatic neurotypical children undergoing diagnostic endoscopy. While disaccharidase deficiency is by no means a unique feature in autism, this finding in persons with ASD suggests it may play an important role in cognitive/behavioral function in conjunction with numerous other pathophysiologic GI activity known to occur in ASD.

INTESTINAL MUCOSAL PERMEABILITY

Intestinal mucosal permeability, or "leaky gut", has been linked to developmental and behavioral changes in children. For example, a study published in 2010 that evaluated alterations in the intestinal barrier in patients with ASD and their first-degree relatives found a high percentage of abnormal intestinal permeability among patients (36.7%) and their relatives (21.2%) as compared to normal subjects (4.8%)[28]. The authors concluded that their results provided support for the leaky gut hypothesis.

A recent 2019 review of the concept of 'leaky gut' discusses how intestinal barrier integrity is commonly measured, what clinical impact a compromised intestinal barrier can have in humans, and sheds light on the nuances of this of this complex topic[29]. Although the review was not specifically about the leaky gut hypothesis in ASD-associated GI disease, the author's conclusion that "clinicians should be aware of the potential of barrier dysfunction in GI diseases and of the barrier as a target for future therapy" is highly relevant to this discussion.

Between 1996-2016 at least five investigations into the frequency and extent of intestinal permeability in children with ASD were published[19,30-33], but the heterogeneity in study design and the exclusion of GI symptomatic children in some of the studies makes it difficult to draw meaningful conclusions as to the contribution of an excessively permeable membrane to cognitive and behavioral dysfunction in children with ASD and inflammatory GI disease. However, taken together, these studies report an overall greater frequency of increased intestinal permeability in ASD as compared to non-ASD controls, though it appears that this finding does not reach statistical significance in the more rigorous studies.

Lastly, in a study investigating blood-brain barrier and intestinal epithelial barrier function, Fiorentino *et al*[34] using duodenal mucosal biopsies from GI-symptomatic children with ASD (n = 12) and healthy controls (n = 9), found that 75% of the ASD samples had reduced expression of barrier-forming tight junction proteins, suggesting an impaired gut barrier integrity.

INFLUENCE OF THE MICROBIOTA

Human health and well-being are inextricably linked to a balanced microbiome and it is well established that intestinal dysbiosis can alter GI physiology, immune function,

and even behavior in children with ASD, a population in which microbial gut dysbiosis is common[35]. In the context of the gut-brain-axis in ASD, the influence of the microbiome is an area of intense interest and research activity. Although published studies report imbalances in intestinal microbiome composition in children with ASD [36-38] and have investigated the relationship between dysbiosis and ASD-related cognition, behavior, and GI symptomatology[39], the mechanisms by which the microbiota are thought to alter GI function and behavior are still actively being investigated. A more comprehensive understanding of mechanisms by which dysbiosis occurs, and how it impacts host function, will accelerate the development of clinically relevant mitigation and therapeutic strategies[40].

CLINICAL ENDOSCOPIC AND LABORATORY OBSERVATIONS/EXPERIENCE OF THE AUTHORS

Serum antibodies to luminal bacterial and fungal microbes

In clinical gastroenterology, the presence of serological antibodies to normal intestinal flora and their association with IBD has been well established. Though not used clinically as a diagnostic tool, the presence of these antibodies distinguishes one form of IBD from another and emphasizes the prominent role of enteric bacteria and fungi as antigenic stimuli in IBD; only rarely are they present in the general and disease control populations. Their presence does not inform specific treatment strategies, but they do suggest an important microbiome related pathogenic pathway for development of intestinal mucosa inflammation in IBD.

To date, there have not been published studies that have investigated the frequency of these serologic markers in ASD-associated IBD. It has been the experience of the authors that, although the frequency with which they are present in ASD-IBD is somewhat less than in CD[41,42], they occur with much greater frequency than in the general population. As with CD, there is age-related appearance of these markers such that the anti-flagellan antibodies are prominent in children under 10 years of age, whereas the anti-glycan antibodies (*e.g.*, ASCA) are more dominant in the teenage and young adult patients[43].

Focal patchy lymphangiectasia

Intestinal lymphangiectasia (the presence of lipid and protein-rich fluid within dilated small intestinal villi) is another endoscopic finding commonly encountered by the authors in teenage and young adult patients with ASD and enteritis who have a long-standing history of untreated gastrointestinal symptoms. Although lymphangiectasia may be found in any number of disease states that prevent the free lymphatic flow away from the intestinal lumen (*e.g.*, elevated central venous pressure secondary to right sided cardiac failure, lymphoma of draining lymph nodes causing distal obstruction, *etc.*), it has also been noted in intestinal inflammatory states such as CD where the obstruction to outward lymph flow occurs in the intestinal wall layers as it does in ASD-enteritis[44]. Examples of intestinal lymphangiectasia in ASD enteritis co-occurring in the same region as classic IBD aphthous ulcers, and in adjacent mucosa in the same patient is presented in Figure 1. To date, the authors have not encountered protein-losing enteropathy resulting from lymphangiectasia.

In the experience of the authors, a third type of endoscopic lesion frequently seen in younger ASD-GI children (less than 10 years of age) is that of white spots, either singular or in clusters, that are prominent in the proximal small bowel and present, but much less frequent, in the distal small bowel (Figure 2). They are often, but not always, seen in conjunction with mildly erythematous mucosa, and inflammatory infiltrate is typically not noted on routine H&E staining. Upon histologic multiple sectioning of the biopsy specimen, truncated villi are noted (single or contiguous) that demonstrate a protective fibrous plume emanating from the core of the decapitated villi. Villous decapitation allows luminal contents to evade the highly evolved system of selective absorption and results in increased permeability (Figure 3). In these cases, capsule endoscopy does not reveal the typical lipid filled villi, but rather a white spot on the surface of the mucosa not within a villous structure.

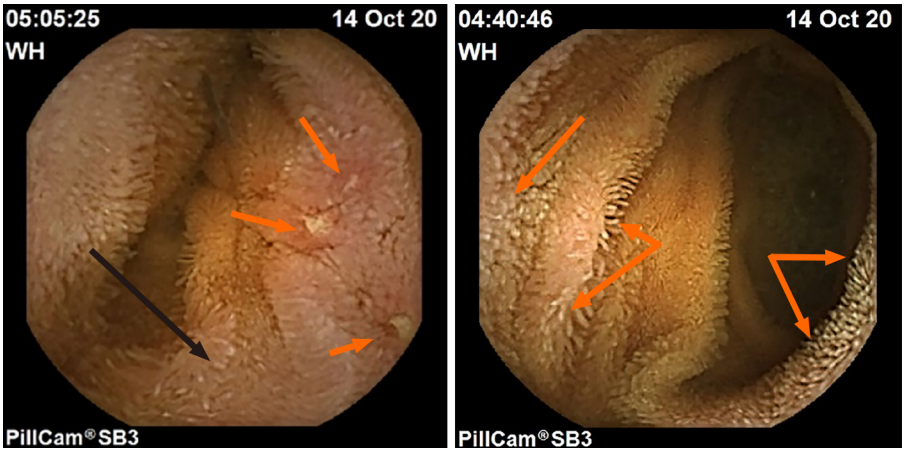


Figure 1 Pillcam images from the small bowel of a gastrointestinal-symptomatic patient with autism spectrum disorder. Lymphangiectasia in patient with autism spectrum disorder-associated enteritis (left panel, black arrow); the patient also exhibited aphthous ulcerations (orange arrows); Jejunal lymphangiectasia (orange arrows) in adjacent mucosa of same patient (right panel).

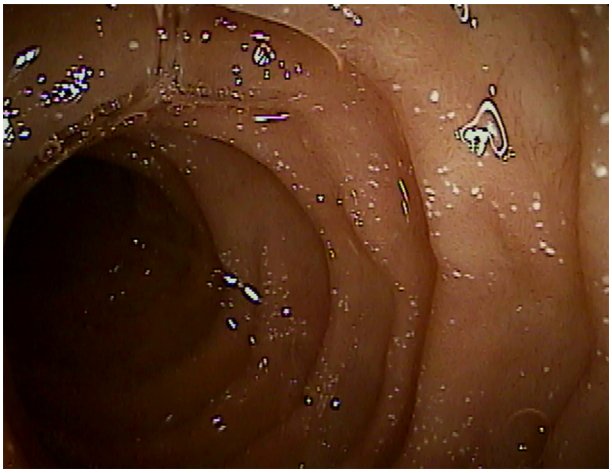


Figure 2 Endoscopic image of white spot lesions of the proximal small bowel in a gastrointestinal-symptomatic child with autism spectrum disorder.

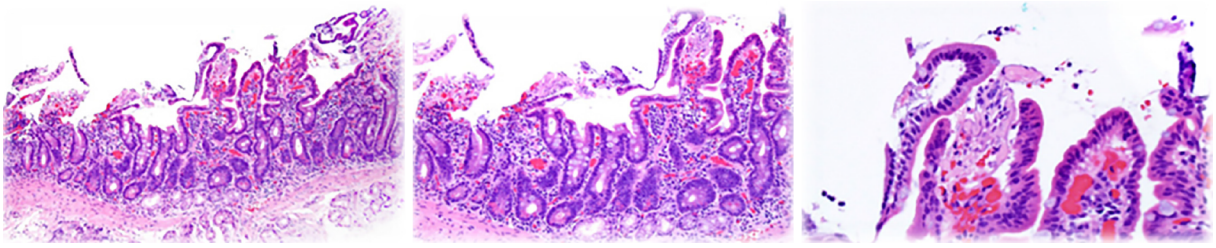


Figure 3 Histologic staining of a mucosal biopsy specimen from the proximal small bowel of a patient with autism spectrum disorder-associated enteritis. White spot lesions (truncated villi) can be seen in low (left); medium (middle); and high magnification (right) of the H&E-stained images.

POTENTIAL MECHANISMS OF CNS INJURY SECONDARY TO UNIQELY INFLAMED GI MUCOSA

Based on the cumulative published literature discussed to this point detailing what is known about the pathology of the inflamed GI mucosa in GI-symptomatic children with ASD, a unidirectional (bowel to brain) mechanism of enterogenous CNS injury in ASD is proposed (Figure 4).

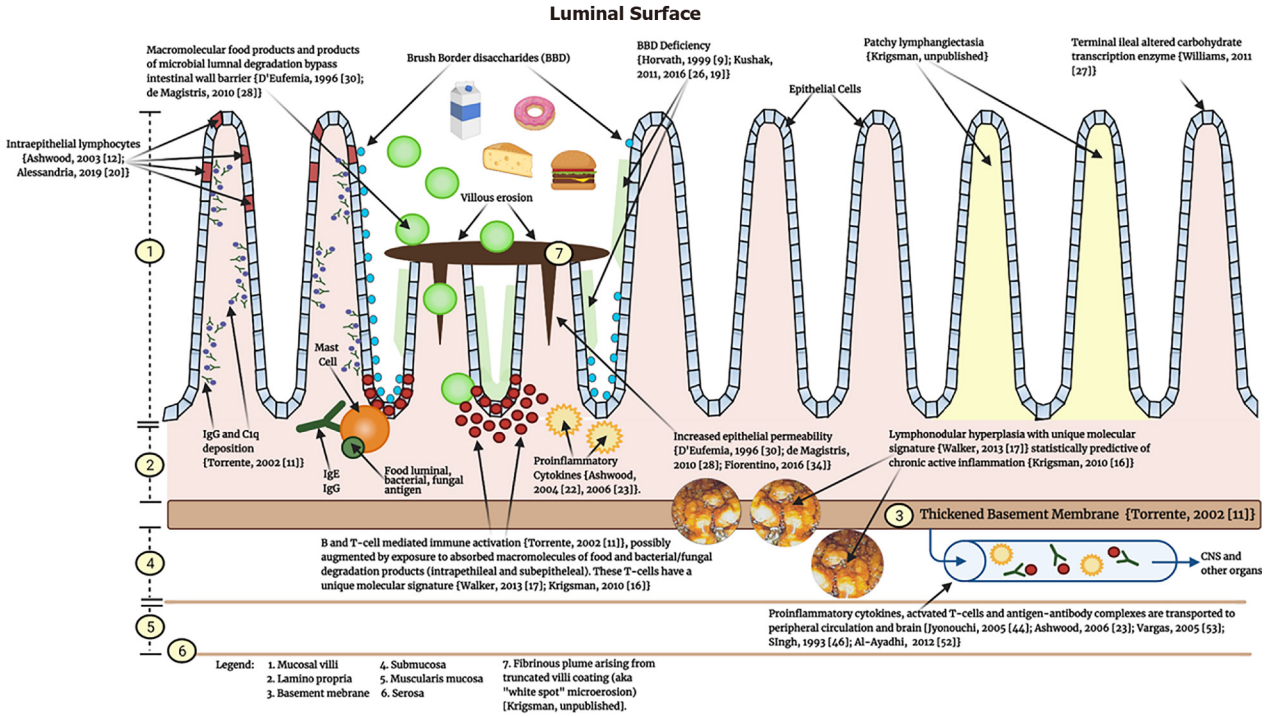


Figure 4 Schematic diagram depicting pathological findings in a portion of the gastrointestinal tract of a representative gastrointestinal-symptomatic child with autism spectrum disorder[9,11,12,16,17,19,20,22,23,26,27,28,30,34,46,52,53]. Key landmarks are identified in the legend (#1-7) and key findings are described throughout the diagram.

For reasons that are not yet entirely clear - but that include environmental, epigenetic, maternal-fetal, and perhaps genetic factors - the immune response in ASD is primed towards over-responsiveness. This over-responsiveness manifests as a heavy lamina propria B and T-cell presence, IgG colocalization with complement c1q on the basolateral enterocyte membrane[11], and intraepithelial lymphocytosis[12,20]. Excessive levels of pro-inflammatory cytokines produced by these cell lineages, as well as deficiencies in counter-regulatory IL-10, are consistently present[22,23]. Marked LNH, a persistently occurring feature of GI immunopathology, is typically present and predicts the presence of cellular inflammation[16]. The combination of hypertrophied reactive LNH and the thickened fibrous basement membrane[11] may serve to obstruct, in whole or in part, lymphatic flow away from the mucosa, resulting in lymphangiectasia. The gene transcriptional profile of the inflammatory infiltrate is unique to children with autism and overlaps significantly with CD[17]. Luminal bacteria are antigens known to be targeted by the mucosal antibodies (Krigsman, unpublished observation).

This persistent inflammatory presence in the intestinal mucosa eventually results in mucosal and epithelial architectural damage. Villous destruction occurs (truncated decapitated villi) with attempts at self-reparation by villous production of a fibrinous covering. Inflammatory villous damage and destruction results, as always, in the loss of resident brush border enzymes[9,26] and increased intestinal permeability[28,30,34]. The clinical implications of the latter two findings are that luminal contents (food, degradation products of resident flora, medications) can more easily evade the highly developed mechanisms for selective absorption and enter the mucosa and capillaries of the GI tract as macro, not micro, molecules, thus exposing the local and systemic immune system to unrecognized antigens. The result of this immunologic activity at the level of the intestinal mucosa is the production of activated B and T cells, as well as numerous pro-inflammatory cytokines, antibodies, and antigen-antibody complexes, that may then enter the peripheral circulation. Once in the peripheral circulation, the effects of such a wide array of active inflammatory activity is largely unknown, but would help explain the observation by Jyonouchi[45] who in 2005 described an increase in GI symptoms and systemic pro-inflammatory cytokines after exposure to specific dietary antigens in GI symptomatic ASD children.

The presence of autoantibodies to the GI epithelium, *i.e.*, autoimmunity, often heralds the formation of autoantibodies directed against other organs as well[46] and thus, the inflammatory activity emanating from the bowel may contribute to the

development of the numerous CNS autoantibodies described in the literature[47-49]. Additionally, cytokines produced locally in the GI mucosa travel peripherally and can cross the blood brain barrier[50].

Of note, the mechanisms of brain inflammation originating in the bowel may be entirely independent of immune dysregulation of peripheral origin that results in production of anti-CNS antibodies or intracranial cellular and molecular mediators of inflammation. The tendency of autoimmune processes to co-exist in the body and even to augment each other has been discussed elsewhere[46].

Finally, although a number of studies have investigated the role of immunomodulating therapy, targeting inflammatory pathways, as a treatment for autism have appeared over the years (reviewed in 51), the focus of the current review is to understand how the existence of a unique inflammatory bowel disease might impact the brain, and, by extension, how treatment of this IBD might ameliorate core symptoms of ASD. Although "classic" IBD such as CD is not known to affect cognition and behavior in the manner described in ASD, the difference may lie in the unique inflammatory features of ASD-associated enteritis that distinguishes it from CD (as already discussed), and the early age of onset of the ASD enteritis, a time when the brain is most susceptible to toxic insult.

CONCLUSION

We have presented a mechanistic concept, based on published pathologic immunologic processes occurring in the gastrointestinal tract of GI-symptomatic children with autism, describing how such pathology may be contributing to the cognitive and behavioral deficits seen in ASD. The logical next step is to conduct a prospective treatment study to determine whether standard immunotherapy for IBD results in improvement in GI symptoms and histologic disease, and if this improvement correlates with improvement in the ASD cognitive and behavioral domains as well.

ACKNOWLEDGEMENTS

We would like to acknowledge and thank the patients and their families for allowing us the opportunity to work with, study, and observe their children. We also thank Ms. Peyton Lee for her efforts on the creation of Figure 4.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 September 19; 11(9): 619-634

DOI: 10.5498/wjp.v11.i9.619

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Evaluating the emotion regulation of positive mood states among people with bipolar disorder using hierarchical clustering

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Author contributions: Chan SHW conceived and guided the study; Liu KHK, Lau C and Fung AOY completed the literature search; Liu KHK, Lau C and Fung AOY coordinated the data collection; Chan SHW and Yu CH performed the statistical analyses; Chan SHW and Tse S wrote and revised the paper; all authors approved the final version of the manuscript.

Institutional review board statement: The study was conducted according to the Declaration of Helsinki and the ethical guidelines established by the University of Hong Kong/West Cluster of the Hong Kong Hospital Authority.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare having no conflicts of interest.

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Abstract

BACKGROUND

People with bipolar disorder (BD) frequently struggle with the recurrence of affective symptoms. However, the interplay between coping mechanism and positive mood state remains under-researched.

AIM

To explore the associations among behavioral approach system (BAS) sensitivity level, coping, and positive mood states among people with BD.

METHODS

Using a cross-sectional study design, 90 participants with BD were presented with four BAS-activating life event scenarios and assessed with regard to their BAS trait sensitivity, coping flexibility, and mood states. A hierarchical clustering method was used to identify different groups with different styles of coping. Multiple hierarchical regression analyses were conducted to examine the mediating and moderating roles of different components of coping on mood states.

RESULTS

A three-cluster solution was found to best fit the present data set. The findings showed that a low mass of coping combined with low BAS sensitivity level protects people with BD from detrimentally accentuating mood states when they encounter BAS-activating life events. Moreover, coping flexibility is demonstrated to mediate and moderate the relationships between BAS sensitivity level and

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author. Participants gave informed consent for data sharing in which the presented data are anonymized and risk of identification is low.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 11, 2021
Peer-review started: March 11, 2021
First decision: July 15, 2021
Revised: July 25, 2021
Accepted: August 18, 2021
Article in press: August, 18, 2021
Published online: September 19, 2021

P-Reviewer: Gazdag G
S-Editor: Gao CC
L-Editor: A
P-Editor: Wang LYT

mood states. Specifically, subduing the perceived controllability and reducing the use of behavioral-activation/emotion-amplifying coping strategies could help buffer the effect of positive affect.

CONCLUSION

The judicious use of coping in emotion regulation for people with BD when encountering BAS-activating life events was indicated. Practical applications and theoretical implications are highlighted.

Key Words: Bipolar disorder; Mood regulation; Cluster analysis; Coping style; Positive emotions

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Core Tip: Individuals with bipolar disorder (BD) essentially fail to regulate their emotions and behavior effectively due to their behavioral approach system (BAS) hypersensitivity. This research, based on the BAS dysregulation theory, explores the dynamic role of coping in emotion regulation for managing positive mood states due to BAS-activating life events. Results show that a low mass of coping combined with low BAS sensitivity level protects people with BD from detrimentally accentuating mood states. Practical applications for the improvement of stress management programs and theoretical implication for the extension of coping frameworks to include positive mood states are highlighted.

Citation: Chan SHW, Yu CH, Liu KHK, Lau C, Fung AOY, Tse S. Evaluating the emotion regulation of positive mood states among people with bipolar disorder using hierarchical clustering. *World J Psychiatr* 2021; 11(9): 619-634
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/619.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.619

INTRODUCTION

Bipolar disorder (BD) is a biologically-based disorder with significant neurobiological underpinnings[1,2]. Nonetheless, the evidence was mixed and independent of the argument for a psychological dimension in explaining the emotion dysregulation of BD[3-5]. One of the fundamental psychobiological features of BD is the behavioral approach system (BAS) sensitivity level[6], which can lay a foundation for understanding the emotion dysregulation in BD. Individuals with high BAS sensitivity levels are significantly more likely to have lifetime BD[7]. In particular, they tend to be over-responsive in relation to reward-relevant environmental cues.

As such, BAS is postulated to be a system that integrates motivational factors, personality traits, and behavioral tendencies entailed in goal-seeking and reward responsiveness (RR)[8]. More specifically, the BAS dysregulation theory[9] proposes that weak regulation of the BAS is involved in the fluctuations between high and low mood that characterize BDs. While the excessive increase in BAS activity leads to manic symptoms, the undue decrease in BAS activity would result in depressive symptoms.

In addition, according to the BAS dysregulation theory, individuals with BD essentially fail to regulate their emotions and behavior effectively due to their BAS hypersensitivity. Specifically, the emotion dysregulation in BD is manifested as excessive variability in BAS activity in response to BAS relevant signals. Thus, BAS is justified as a good measure of emotion dysregulation in which individuals with BD would easily show elevated responses on psychophysiological indices of BAS sensitivity[9-11]. Particularly, BAS hypersensitivity and vulnerability to dysregulation may be an "endophenotype that mediates the effects of the genetic predisposition to bipolar disorder"[12].

Difficulties in achieving positive emotion regulation may contribute to the development of mania in people with BD[13,14]. Thus, exploring strategies in managing positive affects in BD was accordingly called for[15]. Alloy *et al*[12]

proposed different longitudinal predictors of mood states among people with BD along a proximal-distal continuum, starting from the most proximal predictors (prodromes), to recent environmental factors (BAS-relevant life events), and lastly the most distal temperamental features (BAS sensitivity level). However, the model as proposed by Alloy *et al*[6] did not consider the feasible role of coping during the interaction between BAS sensitivity level and BAS-relevant life events.

In essence, coping is a dynamic process that alters according to changing demands and appraisals of situations. In terms of cognitive appraisal, perceived controllability has been seen as one of the key elements[16,17]. With regard to coping patterns, the traditional dimensions include problem-focused and emotion-focused coping[18-20], which can be adaptive in controllable and uncontrollable situations, respectively, according to the good-fit criteria[21]. Regarding coping in BD, previous studies postulated two essential dimensions, one behavioral and one emotional. On one hand, it has been proposed that coping strategies in the behavioral dimension - including "behavioral deactivation" or "behavioral activation" - regulate the mania and depression prodromes, respectively[22-24]. On the other hand, Edge *et al*[25] put forward similar notions but with regard to the emotional dimension. They found that, in response to positive emotions and rewards, people with BD tend to adopt "emotion diminishing" coping strategies instead of "emotion amplifying" coping tactics. This study is therefore focused on exploring the dynamic role of coping in regard to BAS sensitivity level and BAS-relevant life events. Research has indicated the moderating role of stress coping in life events related to BAS[26,27]. When taking BAS dimensions into account, different mood episodes are developed according to the nature of the life events. Therefore, specific coping strategies are necessary for the BAS-relevant life events. In particular, the fit and adaptability of coping should be emphasized. For example, the use of rumination or self-blame can be positively associated with depression, whereas the use of positive appraisal can be negatively associated with these symptoms. Therefore, different forms of coping may help to explain "how" or "why" BAS sensitivity level predicts or causes emotional responses, or meanwhile, it can play a protective role against different BAS sensitivity level as well as BAS-relevant life events.

This study explored the effects of BAS sensitivity levels and coping with BAS-activating life events on mood states among people with BD. Specifically, different clusters were identified in connection with different types of coping strategies. Research has shown that manic BD participants would have a tendency to habitual use of coping strategies more frequently[28] or putting greater effort in spontaneously regulating emotions[29] than healthy controls. Thus, an objective measure of number of coping strategies is implied in this study. Moreover, investigations were performed to test whether coping can play a mediating or buffering role for different BAS sensitivity levels. It was hypothesized that a higher BAS sensitivity level is associated with over-accentuated mood states, in which the use of a higher sense of behavioral-activation/emotion-amplifying (AA) coping should augment the effect on mood states. Alternatively, the use of behavioral-deactivation/emotion-diminishing (DD) coping should further help to regulate heighted mood states.

MATERIALS AND METHODS

Participants

Ethical approval was obtained from the Institutional Review Board of the University of Hong Kong/West Cluster of the Hong Kong Hospital Authority (UW13-176). Ninety participants with BD were recruited from a regional hospital's outpatient clinic. The inclusion criteria were: meeting the criteria cited in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[30] for diagnosis of bipolar I or II disorder; a required state of full remission for more than 2 mo[31], confirmed by the attending psychiatrists and strictly checked with the corresponding medical records; having been educated to primary level or above; being between the ages of 18 years and 65 years; and being of Chinese ethnicity. Psychiatric diagnoses and remissions were strictly checked with medical records in the hospital. People with a comorbid diagnosis of schizophrenia, schizoaffective disorder, substance abuse, organic brain syndrome, or mental retardation were excluded.

Measures

BAS trait sensitivity: This was measured using the behavioral-inhibition system (BIS)/BAS scales[32]. This self-report scale consists of one BIS subscale and three BAS

subscales: RR, drive (D), and fun-seeking (FS). Specifically, RR measures the sensitivity to pleasant reinforcers in the environment, D measures the motivation to follow one's goals, and FS measures the motivation to find novel rewards spontaneously. Higher scores indicate a higher sensitivity level. Adequate internal consistencies (Cronbach's alphas ranging from 0.66 to 0.81) and good test-retest reliabilities (ranging from 0.59 to 0.69) were established for all of the subscales[32-34]. For this study, translations and cultural adaptations of the scale have been made[35]. The internal consistency reliability (Cronbach's alpha) of the subscales was established ranging from 0.70 to 0.78. Specifically, only the three BAS subscales were used for further analysis.

Coping: This was measured using the Coping Flexibility Questionnaire[16,36], which attempts to capture the simultaneous person-situation transactional processes. At first, 10 BAS activation-relevant life event scenarios were developed with reference to the life events scale[37]. These 10 life events have been discussed, agreed upon, and modified by a pilot focus group of people with BD, *i.e.*, all life events were proven to have comparable BAS-activating effects. All of them were role-played and videotaped by the first author (Chan SHW) and a research assistant. Each scenario was role played for a couple of minutes. The character who needs to make decision in coping was clearly presented. Examples of the 10 events include: "At work, your boss gave you a compliment on your work performance" or "You won an important award due to achievement at work." Then, in the actual field study, two compulsory and two elective scenarios, as chosen by the participants, were presented accordingly. As different individuals may have distinct stressful experiences (and may interpret those experiences differently depending on their illness), exposing each individual to the same nature and number of stressful situations could mitigate this problem[12,38]. Besides, in order to enhance the self-determination level of the participants, they were also advised to make a choice on their own; each was asked to choose two extra life-event scenarios that could be more or less related to his or her living condition, on top of the original two designated life-event scenarios.

The coping indices included the following scores: (1) The perceived controllability score. The participants were asked to view the video clips and vividly imagine encountering in real life the situation portrayed in the life event scenarios. Then, they rated the perceived controllability of the life events on a 6-point scale, with a higher score indicating greater perceived controllability. The scores included the average and the variance of the perceived controllability across the four BAS-activating life events; and (2) The coping strategies score. A list of coping strategies was compiled that included strategies of behavioral-activation and behavioral-deactivation coping[22-24], and emotion-amplifying and emotion-diminishing coping[25]. Participants reported their repertoire of coping responses after their cognitive appraisal. The operationalization of the coping strategies score included the mean and variability (variance) in the number of AA copings (sample items include keeping oneself busy, stimulating coping, self- and emotion-focused coping as well as encouraging rewarding activities) and DD copings (sample items include modifying excessive behavior, engaging in calming activities, avoiding rewarding activities, and dampening responses) across the four different life events.

Mood states: Baseline pre-event affective symptoms (including depressive and manic mood) were measured using the Modified Hamilton Rating Scale for Depression (commonly known as the MHRSD)[39] and the Bech-Rafaelsen Mania Scale (commonly known as the BRMS)[40], respectively. Both scales use a standardized interview format, with higher scores representing higher symptom severity. Post-event mood states were measured using the internal state scale (ISS)[41], which consists of four subscales: Activation (ACT), well-being (WB), perceived conflict, and the depression index. Adequate internal consistencies (Cronbach's alphas ranging from 0.81 to 0.92) have been previously established for all of the subscales. The ISS is a self-report instrument that is sensitive to changes in affective states. Higher scores, specifically in the subscales of ACT and WB, indicate elevated mood states. Translations and cultural adaptations of the scale were also carried out[35], and only the ACT and WB subscales were reported for the present study. Specifically, ACT was used to classify hypomanic (ACT ≥ 200) or euthymic (ACT < 200); whereas, WB was used to classify depressed (WB < 125) or non-depressed (WB ≥ 125). The internal consistency reliability (Cronbach's alpha) of the subscales ranged from 0.61 to 0.85. In the present study, Mansell and Lam[42]'s present state version of the ISS was used. The assessment was completed immediately post-mood induction, enabling the tracking of participants' instant mood states following their viewing of the videotaped vignettes.

Sociodemographic factors

Each participant's sex, age, marital status, educational level, employment status, and residential status were recorded; these were the sociodemographic factors used in this study.

Procedures

First, a list of people with BD attending the outpatient clinic at a regional hospital in Hong Kong was generated. Potential participants who met the inclusion criteria were individually approached by the first author (Chan SHW). After signing a consent form, the participants' baseline pre-event affective symptoms and BAS sensitivity levels were assessed. Subsequently, they were shown video clips depicting two compulsory and two elective BAS-activating life events in a random order. Perceived controllability and corresponding coping strategies for each of these life event scenarios were reported. Finally, the participants' overall post-event mood states were assessed. Each participant was offered a coupon worth Hong Kong $20 (or United States $2.50) for taking part in the study.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 24.0 (IBM Corp., Armonk, NY, United States). First, Ward's hierarchical agglomerative clustering method was used to identify the participants' different styles of coping, based on their degrees of perceived controllability and corresponding numbers of coping strategies. The squared Euclidean distance was used as the proximity measure in clustering the data. The stability of the cluster analysis was determined by dendrogram and data visualization method. Cluster differences of various particulars (including BAS sensitivity level, coping, and post-event mood states) were examined through a multivariate analysis of variance or chi-square analysis. A post-hoc Bonferroni's comparison was then employed. *F*-tests were used to assess significant differences between the clusters; partial η^2 values were used to represent effect sizes. To establish evidence of the proposed mediating effect of coping with regard to the relationship between BAS sensitivity level and mood states, the hierarchical regression analyses were carried out according to the procedures advised by Baron and Kenny[43]. Residual plots were checked to determine the random distribution around zero. When determining the moderating effect of coping, hierarchical regression analyses were performed. These strictly followed the procedures recommended by Frazier *et al*[44]. The predictor and moderator variables were standardized to reduce multicollinearity.

RESULTS

General participants' characteristics

A total of 90 participants with bipolar I or bipolar II disorder were successfully recruited for the study (Figure 1). Their mean age was 43.32 years (SD = 11.26), and one-third of them were male (37.7%). Nearly 80% had an educational level above secondary 5. More than a half (55%) were still single, and a majority (80%) were living with others. Regarding employment status, half (50%) were still unemployed. Their relatively low symptom levels resulted in low mean scores of 1.24 and 0.33 in the MHRSD and BRMS, respectively (theoretical ranges of 0-52 and 0-55, respectively). On average, the participants generated 4.56 (SD = 1.93) and 2.24 (SD = 1.31) numbers of AA coping and DD coping, respectively. The associations of all variables in terms of Pearson's correlation are presented in Table 1. Regarding those excluded participants, their mean age was 45 years (SD = 10.34), and nearly 47.3% were male. Within this group, about 63% were unemployed which was comparable with the study group. Thus, there was no significant difference between the consented and non-consented groups.

Identification and comparison of three clusters based on AA and DD coping

To analyze AA and DD coping, a 90 × 12 data matrix was constructed. The unique identification numbers of the 90 participants were entered in the rows, and the raw scores on the perceived controllability of each life event (the first four columns), the number of AA coping (the following four columns), and the number of DD coping (the last four columns) were entered in the columns. There were four sets of three columns, as each participant responded to four life-event scenarios in total. After the data had

Table 1 Correlations of major variables

Variable	BAS_D	BAS_FS	BAS_RR	CTR	AA	DD	ISS_ACT	ISS_WB
BAS_D	1	0.29[b]	0.41[b]	-0.11	-0.05	0.13	0.01	0.02
BAS_FS		1	0.36[b]	0.01	0.18	0.14	0.20	0.07
BAS_RR			1	0.06	0.33[b]	0.30[b]	0.24[a]	0.34[b]
CTR				1	0.42[b]	0.28[b]	0.04	0.30[b]
AA					1	0.57[b]	0.18	0.29[b]
DD						1	0.06	-0.01
ISS_ACT							1	0.70[b]
ISS_WB								1

[a]$P < 0.05$.
[b]$P < 0.01$.
AA: Behavioral-activation/emotion-amplifying coping; ACT: Activation; BAS: Behavioral approach system; CTR: Perceived controllability; D: Drive; DD: Behavioral-deactivation/emotion-diminishing coping; FS: Fun-seeking; ISS: Internal state scale; RR: Reward responsiveness; WB: Well-being.

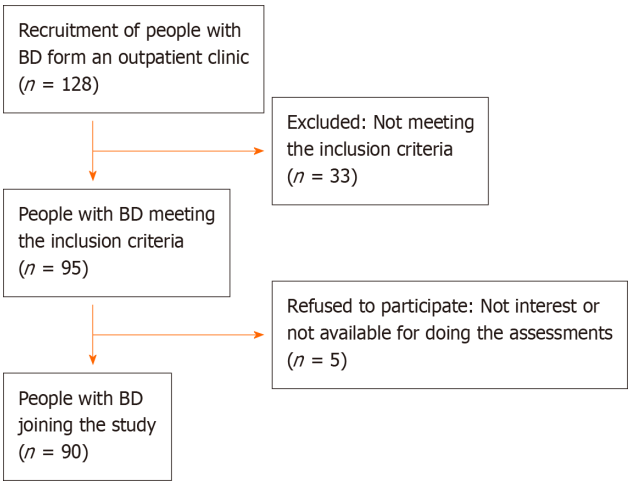


Figure 1 A flow chart of recruitment of participants. BD: Bipolar disorder.

been clustered, a three-cluster solution was found to be the most meaningful and stable (Figure 2 and Table 2). The dendrogram presented in Figure 1 displays all possible options of clustering. In the rightmost part, all participants were grouped together, meaning that there was no clustering at all; whereas, in the leftmost, each participant was paired with another, resulting in too many groups. If there were too many clusters, the subsequent modeling would be too complicated to be interpretable. Conversely, if there were too few clusters (*e.g.*, 2), there would not be distinct coping patterns in each group. This data visualization suggested that the optimal number of clusters should be set at three.

There were no significant differences in the sociodemographic profiles of the three clusters, except in terms of the age of the cluster members. In addition, as long as the baseline affective symptoms were comparable among the three clusters, it was therefore possible to perform further comparison of post-event mood states. Regarding BAS trait sensitivity, there was a statistically significant cluster main effect on the overall BIS/BAS scores (Wilks' $\lambda = 0.798$, $F(6170) = 3.388$, $P = 0.004$, partial $\eta^2 = 0.107$). In further multiple comparisons, an adjusted alpha level of 0.017 (0.05/3) was adopted to correct for the overall Type I errors with regard to three BAS subscales. The members of clusters 1 and 3 were found to be persistent in pursuing their desired goals, as indicated by their significantly higher BAS (D) scores. The members of cluster 1 also had significantly higher BAS (RR) scores than other two clusters; this indicates that their responses to the anticipation of receiving rewards were more positive.

Table 2 Descriptive statistics and comparison of major variables for the three clusters

	Cluster 1, *n* = 26		Cluster 2, *n* = 26		Cluster 3, *n* = 38		
Variables	**Goal achievers with a high mass of coping**		**Goal preservers with a high mass of coping**		**Goal achievers with a low mass of coping**		
	n	**%**	***n***	**%**	***n***	**%**	**Statistics**
Sociodemographic factors							
Sex							χ^2 = 2.13 (P = 0.345)
Female	19	73.1	14	53.8	23	60.5	
Male	7	26.9	12	46.2	15	39.5	
Education level							χ^2 = 7.46 (P = 0.281)
Primary	8	30.8	4	15.4	9	23.7	
Secondary	10	38.4	8	30.8	6	15.8	
Tertiary	8	30.8	14	53.8	23	60.5	
Marital status							χ^2 = 6.72 (P = 0.347)
Single	12	46.2	19	73.1	19	50.0	
Married/cohabited	14	53.8	7	26.9	19	50.0	
Living status							χ^2 = 0.345 (P = 0.987)
Living alone	6	23.0	5	19.3	7	18.4	
Living with others	20	77.0	21	80.7	31	81.6	
Working status							χ^2 = 18.8 (P = 0.171)
Unemployed	17	65.4	11	42.3	17	44.7	
Employed	9	34.6	15	57.7	21	55.3	
	M	SD	M	SD	M	SD	Statistics
Age	48.04	9.64	41.31	12.27	41.47	10.89	F = 3.378 (P = 0.039), 1 > 2, 1 > 3
Baseline affective symptoms							
MHRSD	1.19	1.13	1.38	1.47	1.18	1.25	F = 0.217 (P = 0.805)
BRMS	0.50	1.03	0.38	0.80	0.18	0.56	F = 1.31 (P = 0.275)
BAS sensitivity level							
BAS_D	12.85	1.62	11.62	1.68	12.79	1.76	F = 4.622 (P = 0.012) 1 > 2, 3 > 2
BAS_FS	12.19	2.43	11.42	2.47	11.13	2.70	F = 1.351 (P = 0.264)
BAS_RR	17.85	2.05	15.65	3.11	16.05	2.27	F = 5.924 (P = 0.004) 1 > 2, 1 > 3
Coping							
CTR	2.80	0.74	2.5	0.64	1.68	0.66	F = 23.505 (P < 0.001) 1 > 3, 2 > 3
VCTR	2.70	2.41	1.88	1.10	2.90	2.30	F = 1.998 (P = 0.142)
AA	5.90	1.25	4.68	0.94	2.72	1.27	F = 58.999 (P < 0.001) 1 > 2, 1 > 3, 2 > 3
VAA	1.46	1.83	1.95	1.33	2.08	2.10	F = 0.919 (P = 0.403)
DD	4.28	0.88	2.19	0.61	1.72	0.99	F = 71.542 (P < 0.001) 1 > 2, 1 > 3, 2 > 3
VDD	1.23	0.92	0.94	0.79	0.74	0.62	F = 3.242 (P = 0.044)
Post-event mood states							
ISS_ACT	226.15	99.08	162.31	111.94	182.89	116.90	F = 2.281 (P = 0.108)

ISS_WB	194.62	65.38	139.62	79.22	156.84	77.50	F = 3.728 (P = 0.028)

AA: Behavioral-activation/emotion-amplifying coping; ACT: Activation; BAS: Behavioral approach system; BRMS: Bech-rafaelsen mania scale; CTR: Perceived controllability; D: Drive; DD: Behavioral-deactivation/emotion-diminishing coping; FS: Fun-seeking; ISS: Internal state scale; MHRSD: Modified Hamilton Rating Scale for Depression; RR: Reward responsiveness; VAA: Variance of behavioral-activation/emotion-amplifying coping; VCTR: Variance of perceived controllability; VDD: Variance of behavioral-deactivation/emotion-diminishing coping; WB: Well-being.

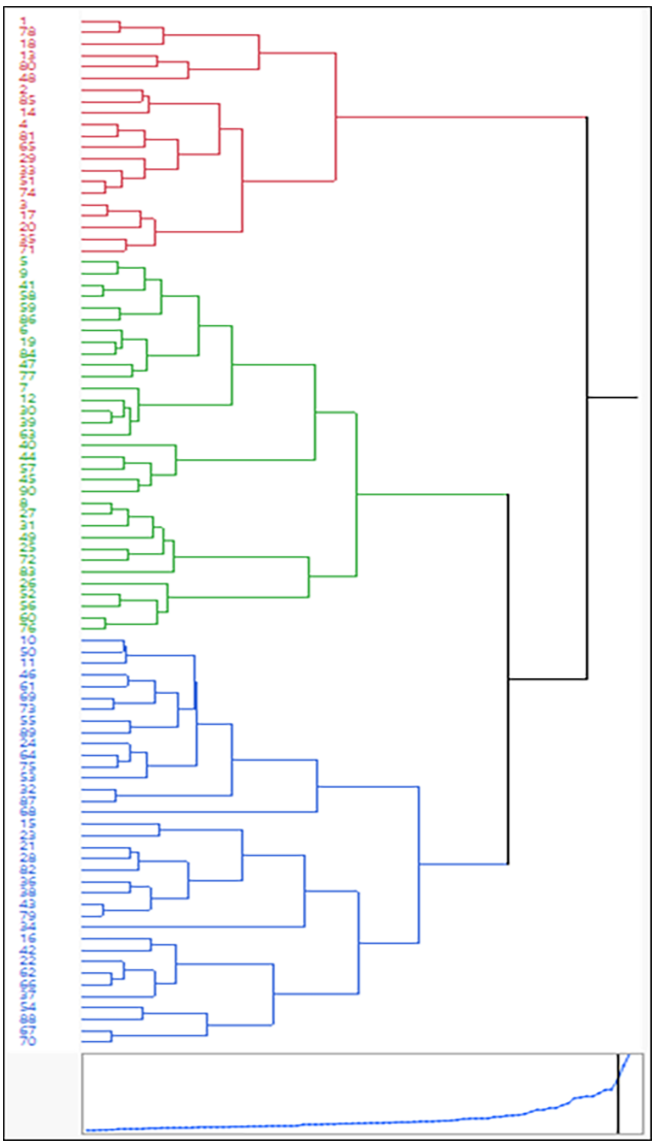


Figure 2 Dendrogram of hierarchical cluster analysis.

Regarding coping scores, there was a statistically significant cluster main effect on the overall scores (Wilks' λ = 0.173, $F(12164)$ = 19.172, P < 0.001, partial η^2 = 0.584). In further multiple comparisons, an adjusted alpha level of 0.008 (0.05/6) was adopted in response to the six different scores that comprised the coping indices. Specifically, the members of cluster 1 (labeled "Goal achievers with a high mass of coping") were characterized by a high level of BAS sensitivity and as using the greatest number of coping strategies with higher degree of perceived controllability. The members of cluster 2 (labeled "Goal preservers with a high mass of coping strategies") were characterized by a low BAS sensitivity level and as using a moderately large number of coping strategies with higher degree of perceived controllability. The members of cluster 3 (labeled "Goal achievers with a low mass of coping") were characterized by a high BAS sensitivity level but also as using the smallest number of coping strategies with lower degree of perceived controllability. For post-event mood states, there was no statistically significant cluster main effect on the overall ISS scores (Wilks' λ = 0.920,

F(4172) = 1.838, *P* = 0.124, partial η^2 = 0.041). However, the members of the "Goal achievers with a high mass of coping" cluster 1 had the highest ISS scores. The effect sizes were small to moderate, as indicated by the partial η^2 values (which ranged from 0.050 to 0.079).

Mediating effect of coping

As the sample size of each cluster was relatively small, the entire sample was used for calculation of the mediation or moderation effects. Following the analyses, only AA coping was found to meet the three conditions stipulated by Baron and Kenny[43]. The results are presented in Table 3. First, ISS (WB) was positively related to BAS (RR) (β = 0.335, *P* < 0.001). When BAS (RR) and AA coping were taken together in the regression analysis, the relationship between BAS (RR) and ISS (WB) was found to be weaker but still significant (β = 0.268, *P* < 0.001). Baron and Kenny[43] suggested that it was a partial mediation model. This partial mediation model was verified by the Sobel *z*-test [45] (*Z* = 2.156, *P* < 0.05).

Moderating effect of coping

The results are shown in Table 4. When the effects of sex and age were controlled for in block 1, some of the components of coping — including AA coping, perceived controllability, and variability of perceived controllability — were found to moderate the association between BAS sensitivity level and mood states. As recommended by Aiken and West[46], simple slope tests were performed to compare the effect of BAS sensitivity level on the mood states of individuals with high (1 SD above the mean) and low (1 SD below the mean) levels of coping. The results showed that the associations between BAS sensitivity level and mood states were negative among individuals with low levels of coping including AA coping, perceived controllability, and variability of perceived controllability (β = -0.735 to -0.019), whereas the associations were positive among individuals with high levels of coping (β = 0.202 to 0.497).

DISCUSSION

This study demonstrates how the judicious use of coping can help in emotion regulation for people with BD when encountering BAS-activating life events. Echoing previous research findings, it was found that higher BAS sensitivity levels[6,11] resulted in higher mood states. By comparing individuals between clusters 1 and 2, it was demonstrated that a higher degree of perceived controllability and using higher numbers of coping strategies can further over-activate an individual's mood state. Alternatively, when comparing clusters 1 and 3, with similar levels of BAS sensitivity, a lower degree of perceived controllability and using lower numbers of coping strategies were found to regulate heightened mood states.

With regard to the cognitive appraisal in terms of the high degree of perceived controllability, the judgment on an appraisal in the coping process may be colored by individual affective state[47], which should be related to the BAS sensitivity level, as shown in this study. Perceived controllability may connote taking an active role or exerting effort to alter the environment. Therefore, reducing the perceived controllability of life events seems to imply the notion of "non-striving," which is one of the core ideas in mindfulness[48-50]; as such, it is no wonder that mindfulness-based intervention is a plausible way to enhance mood regulation in BD[51].

Particularly, the mediation model showed that if an individual has a higher level of BAS sensitivity, this results in over-activation of mood states by stimulating the use of AA coping strategies. These results supplement previous findings[6,12,34] by verifying the role of the BAS dysregulation system in people with BD. The emotion amplifying intention is also in line with the findings of Stange *et al*[52], who suggested that individuals with high levels of BAS sensitivity exhibit greater emotion-focused rumination that may result in manic/hypomanic-like symptoms.

In addition, the moderation model suggests that subduing the use of AA coping, perceived controllability, and variability of perceived controllability was advantageous for people with high levels of BAS sensitivity, as it prevents the detrimental accentuation of mood states. That is, to attenuate their mood states, individuals with high levels of BAS sensitivity should utilize relatively less strategies — such as keeping oneself busy or encouraging rewarding activities — after exposure to BAS-activating life events. This kind of adaptation in coping should also extend the application of the dual process theory of coping flexibility[53] in mood regulation for people with BD. However, the alternative approach of increasing use of DD coping

Table 3 Mediating effect of behavioral-activation/emotion-amplifying coping between behavioral approach system sensitivity level and mood states (with dependent variable as internal state scale_well-being)

Variables	*B*	*SE B*	*β*
Step 1			
Outcome: ISS_WB			
Predictor: BAS_RR	9.841	2.953	0.335[b]
Step 2			
Outcome: AA			
Predictor: BAS_RR	0.244	0.074	0.332[b]
Step 3			
Outcome: ISS_WB			
Mediator: AA	8.054	4.186	0.202[a]
Predictor: BAS_RR	7.873	3.084	0.268[b]

[a]$P < 0.05$.
[b]$P < 0.01$.
AA: Behavioral-activation/emotion-amplifying coping; BAS: Behavioral approach system; ISS: Internal state scale; RR: Reward responsiveness; WB: Well-being.

could not be confirmed from the present results. Perhaps people with BD may tend to avoid use of some strategies, such as dampening response, by classifying them as maladaptive strategies[14]. Some individuals may even express ambivalence towards self-help strategies for the managing of high mood episodes[54]. It is necessary for there to be further investigation into the effectiveness of interventions for BD that emphasize the utilization of DD coping.

Nevertheless, cautions have to be taken in interpreting the findings. A general BAS sensitivity level and overall mood states were used for discussion here, despite there being different subscales presented in the BAS scale or ISS. There could exist a differential relationship between different subscales. ISS (WB) was found to be the common significant outcome in both mediation and moderation models; yet, the predictors involved were distinct. Only BAS (RR) was found in the former; whereas, BAS (D) and BAS (FS) were indicated in the latter. Perhaps the AA coping can be used to explain the contributing reason of sensitivity towards pleasant reinforcers leading to increased mood states. On the other hand, the reduced use of AA coping or perceived controllability can help to reduce the effects on elated mood due to motivation to goals or rewards. Future research is worthwhile for investigating the differences of various BAS or mood states' representation, especially for the mediating or moderating roles of coping. Moreover, videos were used as stimuli in this study. Despite having been found to be a reliable means by which to induce positive mood change[55], future research can be considered to compare different natural *vs* artificial means for eliciting varied mood states.

People who experience positive affect should have better psychological health, but over-elevated mood may not be adaptive for people with BD[56]. The judicious use of coping appears to be vital in managing positive affect or over-elevated mood among people with BD. Originally, the framework of coping was applied only to "negative" or stressful life events[57,58]; applying this framework to "positive" life events, as in the present study, has the potential to generate another conceptual viewpoint. Undoubtedly, people "cope" with positive events in order to cultivate higher positive affect and greater life satisfaction[59,60]. Folkman and Moskowitz[61] have also highlighted the beneficial effect or adaptational significance of positive affect in the midst of stress. However, positive affect as induced by positive events may do harm to people with impaired emotion regulation[37,62]. Coping with both positive effect and negative affect play equivalent roles in cases of people with BD. Broadening models of coping in the present study will help people with BD to gain greater insight into enhancing their competencies in emotion regulation.

This study also has important clinical significance and practical implications for the improvement of stress management programs for people with BD. Conventionally, and in most previous programs[63,64], participants have learned only general coping

Table 4 Moderating effect of coping between behavioral approach system sensitivity level and mood states (with dependent variable as internal state scale_well-being)

Variables	*B*	*SE B*	*β*	R^2	R^2 change	*F* change
Moderator: AA coping						
Block 2				0.137	0.069	3.405[a]
BAS_D	-0.236	7.417	-0.003			
AA	15.417	7.861	0.200			
Block 3				0.234	0.097	10.609[b]
BAS_D × AA	24.777	7.607	0.323[b]			
Moderator: CTR						
Block 2				0.153	0.085	4.256[a]
BAS_D	1.107	7.552	0.014			
CTR	18.150	7.757	0.236[a]			
Block 3				0.214	0.061	6.570[a]
BAS_D × CTR	16.691	6.512	0.258[a]			
Moderator: VCTR						
Block 2				0.086	0.019	0.864
BAS_FS	7.192	8.021	0.093			
VCTR	8.918	7.934	0.116			
Block 3				0.142	0.056	5.437[a]
BAS_FS × VCTR	-15.334	6.576	-0.239[a]			

[a]$P < 0.05$.
[b]$P < 0.01$.
AA: Behavioral-activation/emotion-amplifying coping; BAS: Behavioral approach system; CTR: Perceived controllability; D: Drive; FS: Fun-seeking; ISS: Internal state scale; VCTR: Variance of perceived controllability; WB: Well-being.

skills but not situation-specific ones. Enhancing individuals' understanding of how to differentiate effectively between various stressful situations may enhance their use of coping. Moreover, the emphasis of such a program has typically focused on negative life events. In fact, positive life events also play a significant role for people with BD with regard to life stress in general. This study promotes maintaining the balance of helping people with BD to cope with the later. Taking into account an individual difference in BAS sensitivity level, people with BD can deploy appropriate coping strategies to meet the different challenges that arise from various stressors. For example, "low degree" coping may help to stabilize the mood state of an individual with BD in situations where they are exposed to BAS-activating life events. Echoing the findings of Edge *et al*[25] that people with BD intentionally find appropriate ways to avoid mania so as to allow them to stay well[65], modification of such individuals' coping repertoire should lead to beneficial changes in their mood states. Thus, teaching the judicious use of various coping strategies in terms of AA or DD coping as well as facilitating proper attitude in reducing perceived controllability can further enhance the treatment effects of the stress management program for BD.

This study had some notable limitations. First, "polarity-specific" life events[66,67] either activate or deactivate the BAS in a dynamic process. However, this study focused only on a single pathway with respect to BAS-activating life events. Second, this study examined only people with BD, without a control group for comparison. People without BD should have lower BAS trait sensitivity levels, which may require a less emotion-driven consideration, so it may bring in a distinctive representation for individuals without BD. In addition, persistent cognitive deficits are common in people with BD even when they are euthymic[68], in which ventrolateral prefrontal cortex dysfunction was also demonstrated as a trait-related abnormality in people with euthymic BD[69]. Thus, future studies that compare euthymic BD with a healthy control group regarding the decision making in choosing coping strategies would be

of interest. Third, because only cross-sectional correlation statistics were utilized in this study, no definitive statement on causality can be made. Using a lower number of coping strategies can regulate heightened mood states, but it is also possible that the effect goes the other way around. Further longitudinal research is needed to achieve an understanding of the directionality. Moreover, the small sample size of this study may have affected the findings. In particular, the size of each cluster was quite small, and this may have affected the validity of the findings.

Despite these limitations, this study does provide novel insights into the landscape in which BAS sensitivity level and coping affect the mood states of people with BD. Investigations of this kind significantly improve our ability to identify potential vulnerabilities or protective factors that influence the course of recovery for people with BD. BAS-activating life events have been reckoned to have a prospective association with people's propensity to experience increasingly severe manic symptoms[33]. Thus, people with BD may be likely to over-activate their positive emotions or develop manic/hypomanic mood symptoms after exposure to the corresponding events. In essence, BD is characterized by amplified emotionality[13] together with difficulty in regulating emotion[70,71]. The ability to regulate their emotions, using appropriate coping strategies for various different life events, is therefore of paramount importance for people with BD.

CONCLUSION

Using a small number of coping strategies appears to be an adaptive emotion regulation strategy[72] for maintaining an euthymic state for people with BD. More specifically, as shown in this study, reducing the use of AA coping should be effective in countering high BAS sensitivity level, especially when coping with BAS-activating life events.

ARTICLE HIGHLIGHTS

Research background

Individuals with bipolar disorder (BD) frequently struggle with the recurrence of affective symptoms. However, the interplay between coping mechanism and positive mood state remains under-researched.

Research motivation

To add to the current knowledge about the role of coping in emotion regulation in people with BD.

Research objectives

The main objective was to explore the associations between the behavioral approach system (BAS) sensitivity level, coping flexibility, and mood states among people with BD after they encounter BAS-activating life events.

Research methods

Using a cross-sectional study design, 90 participants with BD were presented with four BAS-activating life event scenarios and assessed with regard to their BAS trait sensitivity, coping flexibility, and mood states. A hierarchical clustering method was used to identify different groups with different styles of coping. Multiple hierarchical regression analyses were conducted in order to examine the mediating and moderating roles of different components of coping on mood states.

Research results

A three-cluster solution was found to best fit the present data set. The findings showed that a low mass of coping combined with low BAS sensitivity level protects people with BD from detrimentally accentuating mood states when they encounter BAS-activating life events. Moreover, coping flexibility is demonstrated to mediate and moderate the relationships between BAS sensitivity level and mood states. Specifically, subduing the perceived controllability and reducing the use of behavioral-activation/emotion-amplifying coping strategies could help buffer the effect of positive affect.

Research conclusions

The judicious use of coping in emotion regulation for people with BD when encountering BAS-activating life events was indicated.

Research perspectives

The findings of this study have practical implications for the improvement of stress management programs. Theoretically, this study helps integrate the concept of coping flexibility into the BAS dysregulation theory as it applies to mental illness.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 September 19; 11(9): 635-658

DOI: 10.5498/wjp.v11.i9.635

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Thinking about worry: A systematic review and meta-analysis on the assessment of metacognitions in children and adolescents

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Author contributions: Köcher LM and Christiansen H designed the research; Köcher LM performed the research; Köcher LM and Schneider K analyzed the data; Köcher LM wrote the paper; Christiansen H and Schneider K supervised the paper; All authors read and approved the final manuscript.

Conflict-of-interest statement: None of the authors has any conflict of interest to declare.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

The metacognitive model of generalized anxiety disorder identifies three forms of metacognition: Positive metacognitive beliefs about worry (POS), negative metacognitive beliefs about worry (NEG), and meta-worry. Though this model was originally developed relying on adult samples, it has since been applied to children and youth in different studies, and results mostly support its validity for this group. As the roles of POS, meta-worry, and age-effects do not appear to be fully clarified for children and adolescents yet, an integration of studies on children and adolescents and the metacognitive model is both timely and worthwhile.

AIM

To summarize the current research on relationships, age-effects, and measurements for POS, NEG, and meta-worry in childhood and youth.

METHODS

We carried out a literature search in the electronic databases PsycINFO, PubMed, PSYNDEX, and ERIC in 2017 and updated in 2020. Empirical research in German or English language on metacognition was included with child and adolescent samples diagnosed with anxiety disorders or healthy controls if POS, NEG, or meta-worry were measured. Studies were included for meta-analysis if they reported correlations between these metacognitions and anxiety or worry. Consensus rating for eligibility was done for 20.89% of full-texts with 90.32% agreement. Risk of bias was assessed with the appraisal tool for cross-sectional studies and consensus rating of appraisal tool for cross-sectional studies for 20.83% of included studies attaining agreement of intraclass correlation = 0.898. Overall, correlations between metacognitions, anxiety and worry were calculated with RevMan 5.4.1, assuming random-effects models. Meta-regressions with

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Manuscript source: Invited manuscript

Specialty type: Psychology

Country/Territory of origin: Germany

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: April 21, 2021
Revised: May 4, 2021
Accepted: July 27, 2021
Article in press: July 27, 2021
Published online: September 19, 2021

P-Reviewer: Moradi L
S-Editor: Liu M
L-Editor: Filipodia
P-Editor: Wang LYT

mean age as the covariate were performed *via* the online tool MetaMar 2.7.0. PROSPERO-ID: CRD42018078852.

RESULTS

Overall, k = 763 records and k = 78 additional records were identified. Of those, k = 48 studies with 12839 participants were included and of those, k = 24 studies were included for meta-analysis. Most studies showed consistent NEG correlations with worry and anxiety, as well as higher values for clinical than for non-clinical samples. POS findings were less consistent. Meta-analysis revealed large effects for NEG correlating with worry and anxiety, small to medium effects for POS correlating with worry and anxiety, as well as small to medium effects for POS correlating with NEG. Meta-regressions did not reveal mean age as a significant covariate. Meta-worry was assessed in only one study. We identified eight questionnaires and one interview-format that assess metacognition about worry in children and adolescents.

CONCLUSION

POS and NEG are measurable from the age of seven upwards and correlate with anxiety and worry without influences by age. Meta-worry requires further investigation.

Key Words: Metacognition; Anxiety; Child; Adolescent; Measures; Meta-analysis

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Core Tip: Systematic review and meta-analysis showed that positive metacognitive beliefs about worry and negative metacognitive beliefs about worry correlate with worry and anxiety, as claimed in the metacognitive model of generalized anxiety disorder. Studies tended not to report significant correlations between age and positive metacognitive beliefs about worry or negative metacognitive beliefs about worry. Mean age was not a significant covariate in meta-regressions. No conclusions about meta-worry's influence can be drawn. We need an adequate measurement of meta-worry, and measurements applying to young children should undergo further investigation. Studies showed moderate to large heterogeneity, and the power of meta-regression might have been low. As mostly cross-sectional data were collected, no causal conclusions can be drawn.

Citation: Köcher LM, Schneider K, Christiansen H. Thinking about worry: A systematic review and meta-analysis on the assessment of metacognitions in children and adolescents. *World J Psychiatr* 2021; 11(9): 635-658
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/635.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.635

INTRODUCTION

Anxiety disorders in children and adolescents reveal a 6.5% prevalence, making them the most prevalent mental disorder in this age group worldwide[1]. They are associated with various negative effects, *e.g.*, impaired school performance, sleep and social functions, increased risk of comorbidities (such as depression or other anxiety disorders), and persistence into adulthood[2-5]. A key feature of anxiety is worry. Worries are understood as repetitive, chained thoughts about potentially negative future events, and they are fear-related[6,7]. These thoughts are common, occurring in 60.1% of children and adolescents[8]. Almost every second preschooler has worries, and even more children worry as they grow older[9]. Worry is associated with anxiety symptoms in community samples as well as in samples consisting of children with anxiety disorders[10,11]. Children with anxiety disorders suffer more intense worries than healthy children[12]. The frequency of worry itself, however, does not seem to be problematic. However, worries seem to become pathological when they are experienced as intense and uncontrollable[13]. Excessive worry is a core criterion of

general anxiety disorder (GAD)[14], and domain-specific worries are a diagnostic criterion of separation anxiety disorder (SAD)[13]. When compared specifically, children with diagnosed anxiety disorders reveal significantly more self-reported worry than healthy children, and children with GAD scored higher on worry assessments than children suffering from other anxiety disorders[11]. Worry is thus a central feature of anxiety in childhood and youth.

In line with the importance of evaluating worries as intense and uncontrollable, both worry itself and "thinking about worry" play key roles in anxiety disorders. Such higher-level thinking is described as metacognition, a concept first defined by Flavell [15] as "knowledge and cognition about cognitive phenomena" (S. 906). Metacognitions are known to be involved in the development and maintenance of mental disorders such as depression and anxiety or obsessive-compulsive disorders (OCD) [16-20]. For pathological worries to develop, Wells[19-21] emphasizes three forms of metacognition that play decisive roles: Positive metacognitive beliefs about worry (POS), negative metacognitive beliefs about worry (NEG), and meta-worry. POS refer to the usefulness of various thoughts (*e.g.*, "Worrying helps me to avoid problems in the future"[22]). NEG can be understood as trait-beliefs that a person generally holds about worries[21]. They include the appraisal of one's own thoughts as uncontrollable and imply negative consequences of worries (*e.g.*, "Worrying is dangerous for me"[22]). Meta-worry can be described as the state of worrying about worry[21]. Wells describes his assumptions about how these metacognitive constructs interact with each other and with worry, behavior, thought control strategies, and emotion in the metacognitive model of GAD[19-21].

The metacognitive model of GAD postulates that an intense, negative thought is what initially triggers worry. Worrying is then especially likely to become a coping strategy when someone tends to think about worry's usefulness (POS). If general beliefs that worry is dangerous or uncontrollable (NEG) have been activated, one starts to worry about current worries (meta-worry). Meta-worry provokes emotions such as anxiety, which only exacerbates worry and meta-worry. Anxiety is misattributed as a consequence of the worries themselves, which in turn reinforces NEG. As this thought spiral continues, meta-worry triggers coping strategies such as reassurance, avoidance behavior, or substance abuse. As these dysfunctional attempts prevent the person from experiencing that worries are controllable and harmless, meta-worry and NEG about the danger of worries are reinforced. Meta-worry can also lead to thought-control strategies such as suppression, and if these fail, meta-worry and NEG will persist (for details and figural display of the metacognitive model of GAD see Wells[21]).

The metacognitive model has been investigated in children and adolescents in different studies. Esbjørn *et al*[23] showed that metacognitive processes, in addition to the effects of gender, age, and anxiety, account for 14% of the variance of worry and an additional 11% of the variance of anxiety in a healthy sample of children. In a second study, patients with GAD reported more POS and NEG than children with other anxiety disorders or healthy controls, and children with anxiety disorders reported more NEG than healthy controls[23]. Another study by Ellis and Hudson[24] also showed that adolescents with anxiety disorders described more POS and NEG than a control group. These findings support assumptions of the metacognitive model of GAD and support its validity in childhood and youth. However, there are also contradictory findings that question this validity. For example, some studies failed to detect any significant relationships between POS and worry or anxiety in children[25,26] or found no differences in either POS or NEG between clinical and non-clinical participants[27,28].

In addition, the question arises as to the age that these metacognitions about worry develop and whether they change with age. Ellis and Hudson[29] noted that few studies on the metacognitive model included children under 12 years of age. There have also been mixed results about the relationship with age, as some studies show correlations between metacognitions and age[24] while other studies do not[30]. When transferring adult models like the metacognitive model of GAD to children, the experience and cognitive skills of children must be taken into account[24]. Metacognitive skills are assumed to be gradually acquired[31]: At 3 years of age, children can name mental processes and distinguish them from the external environment[32,33]. From the age of four, children understand that thoughts can refer to non-real or non-present things[34]. Seven-year-old children know when, what, and at what frequency they themselves or others are thinking[33-35]. However, more recent results indicate that already 3- to 5-year-old children can demonstrate metacognitive knowledge when measured with an age-appropriate interview[36].

To evaluate the age at which children first think about their worries (*i.e.* metacognition about worry), an age-appropriate assessment is needed. Many studies use questionnaires to measure metacognition in children[23,24,27]. However, a recent review's authors concluded that questionnaires for younger children yield mixed results for factor structure, internal consistency, and age-appropriateness, and they emphasize the need for further development and psychometric analysis of assessments for metacognition in childhood[37].

The present systematic review synthesizes the latest findings about metacognition on worry in children and adolescents. Current knowledge for POS, NEG, and meta-worry as well as their development is summarized, as are available assessments of POS, NEG, and meta-worry for children and adolescents. In so doing, we posed the questions below:

What evidence is there for positive relationships between POS, NEG, and meta-worry with each other and with worry and anxiety in children and adolescents?

At what age do children report POS, NEG, and meta-worry, and does age play any role in relationships with worry and anxiety?

Which methods are currently applicable to assess POS, NEG, and meta-worry in childhood and youth?

To answer these questions, we conducted a systematic review of the recent literature. We synthesized the tested relationships between POS, NEG, meta-worry with each other, worry, and anxiety in order to compare those results with the postulated relationships in the metacognitive model of GAD. For further validation, we compared non-clinical samples and clinical samples consisting of children and adolescents with anxiety disorders, as the latter are likely to exhibit more NEG and meta-worry according to the metacognitive model of GAD, while that does not necessarily apply to POS (compare Wells[21]). To assess potential age effects, we summarized results for age of onset and developmental patterns for POS, NEG, and meta-worry. Different methods of assessing POS, NEG, and meta-worry and reported reliability measures, their usage in age-ranges, and the numbers of studies are resumed.

Depending on the studies identified, we conducted additional meta-analysis based on effect sizes of POS, NEG, and meta-worry correlations with each other and with anxiety and worry. Whenever possible, we performed meta-regressions to analyze whether age is a significant covariate for these relationships.

MATERIALS AND METHODS

Literature search

This systematic review was registered with PROSPERO (International prospective register of systematic reviews, PROSPERO-ID: CRD42018078852, last update: January 26, 2021) and is based on the PRISMA Statement[38] and the PRISMA-P Statement [39]. The literature search was first run on September 24, 2017 and updated on February 6, 2020.

The search string "(children OR adolescents*) AND (meta cognition* OR metacognition* OR meta-cognitive belief* OR meta cognitive belief*) AND (anxiety OR worry OR phobia)" was used in the following databases: PsycINFO, PubMed, and PSYNDEX. In addition, available full-texts of the database ERIC were searched with the same search string. In the first search (2017), we set no limitations to obtain a preferably broad impression of the state of research. In the second search (2020), the period was limited to publication dates between 2017 and 2020. We identified additional studies through a backward search of reference lists by screening additive publications of research groups and, to include the gray literature, the screening of doctoral theses. After identifying records through the databases and additional searches, duplicates were removed. Afterwards, titles, key words, and abstracts in all records were screened by the first author. The full-text versions of the remaining records were analyzed for eligibility. Doctoral theses were only included if the data had not been published in a journal. In case of the latter, the publication was included and the doctoral thesis was excluded from analysis. The study selection process was conducted by one reviewer (Köcher LM). Additionally, 20.89% (k = 33) of the full-texts were independently rated for eligibility by another reviewer (Schneider K). Overall, 90.32% of the ratings were in agreement. In case of discrepancies, a third reviewer (Christiansen H) was consulted, and consensus was reached for the remaining 9.68% (k = 3) of records.

Study selection

Empirical studies reporting quantitative data were included in the systematic review, which fulfilled the following criteria: (1) Participants were 18 years of age or younger; (2) Non-clinical samples and/or clinical samples with anxiety disorders were investigated. We followed the classification for anxiety disorders in the fifth edition of the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-5)[40], including the following diagnoses: GAD, SAD, social anxiety disorder (SoD), specific phobia, agoraphobia, and panic disorder; (3) POS, NEG, and/or meta-worry were assessed as an outcome variable; (4) The study was published in English or German language; and (5) The study had been published by February 6, 2020.

To be included in our meta-analysis, studies also had to fulfill these criteria: (6) Bivariate correlation coefficients for relationships between POS/NEG/meta-worry with each other/anxiety/worry were reported; and (7) Data were not reported in a study that had already been included in our meta-analysis.

Data extraction

The first author extracted the following information from the included studies: Author(s), year of publication, title, country, study design, sample size, study population (non-clinical and/or clinical, and related diagnoses), participants' age range and/or mean age, gender distribution, measurement of POS/NEG/meta-worry and reliability, anxiety measurement, worry measurement, relationship of POS/NEG/meta-worry with each other/anxiety/worry/age, and group differences between clinical and non-clinical subgroups in POS/NEG/meta-worry.

The study characteristics coded for meta-analysis and meta-regression by the first author were: Effect sizes of correlations between POS/NEG/meta-worry with each other/anxiety/worry, sample size, and mean age. If studies reported correlational coefficients split for different subgroups such as male or female participants, or clinical or non-clinical participants, correlations were coded separately for subgroups and then combined to a single correlation according to the following procedure: Correlations were transformed into Fisher's z scores and weighted by subsample size, then the mean of both values was inversely z-transformed into product-moment-correlation coefficients. If a study reported a subsample's data in a previous study that we had already included in the meta-analysis, only the other subsample's data were coded for this study. For meta-regressions, studies were only included if they reported the mean age of their samples. If mean age was reported for split subgroups, values were coded for each of these subgroups and mean of the mean ages, weighted by subsample sizes, was calculated and used for meta-regression.

Risk of bias

To assess the risk of bias, each study was rated on the Appraisal tool for Cross-Sectional Studies (AXIS)[41] by one reviewer (Köcher LM). AXIS-scores range between 0 and 20 and were clustered in the categories high (0-6), moderate (7-13), and low risk of bias (14-20) for a global rating. Additionally, 20.83% of studies (k = 10) were rated by an independent reviewer in our working group. Our interrater agreement (intraclass correlation = 0.898) can be considered as good[42].

Statistical analysis

Statistical analysis was performed by the first author and reviewed by the third author at the Department of Psychology, Philipps University Marburg. Coded correlation coefficients were transformed into Fisher's z scale for meta-analysis. For reports of summary correlations, all summary Fisher's z were back-transformed into Pearson's product-moment correlations. Cohen's criteria[43] were used to interpret overall effect sizes. Random-effect models were used for analysis because of assumed heterogeneity in addition to sampling error. Calculations were computed using the computer program RevMan, version 5.4.1[44]. To show actual dispersion of overall effects, prediction intervals are reported in addition to CIs, as proposed by IntHout *et al*[45], and calculated based on the T^2-estimate[46]. Heterogeneity was tested using Q-statistic and I^2. Interpretations of I^2 are based on benchmarks proposed by Higgins *et al*[47]. Results of each meta-analysis are graphically illustrated in forest plots. A set of meta-regressions was conducted to test whether mean age of the included studies moderated the analyzed correlations significantly. Other potential covariates such as sample type (clinical *vs* non-clinical) were not examined due to the low number of k = 1 study[25] included in the meta-analysis with a clinical sample only. Meta-regressions were run using the free online meta-analysis tool Meta-Mar, version 2.7.0[48].

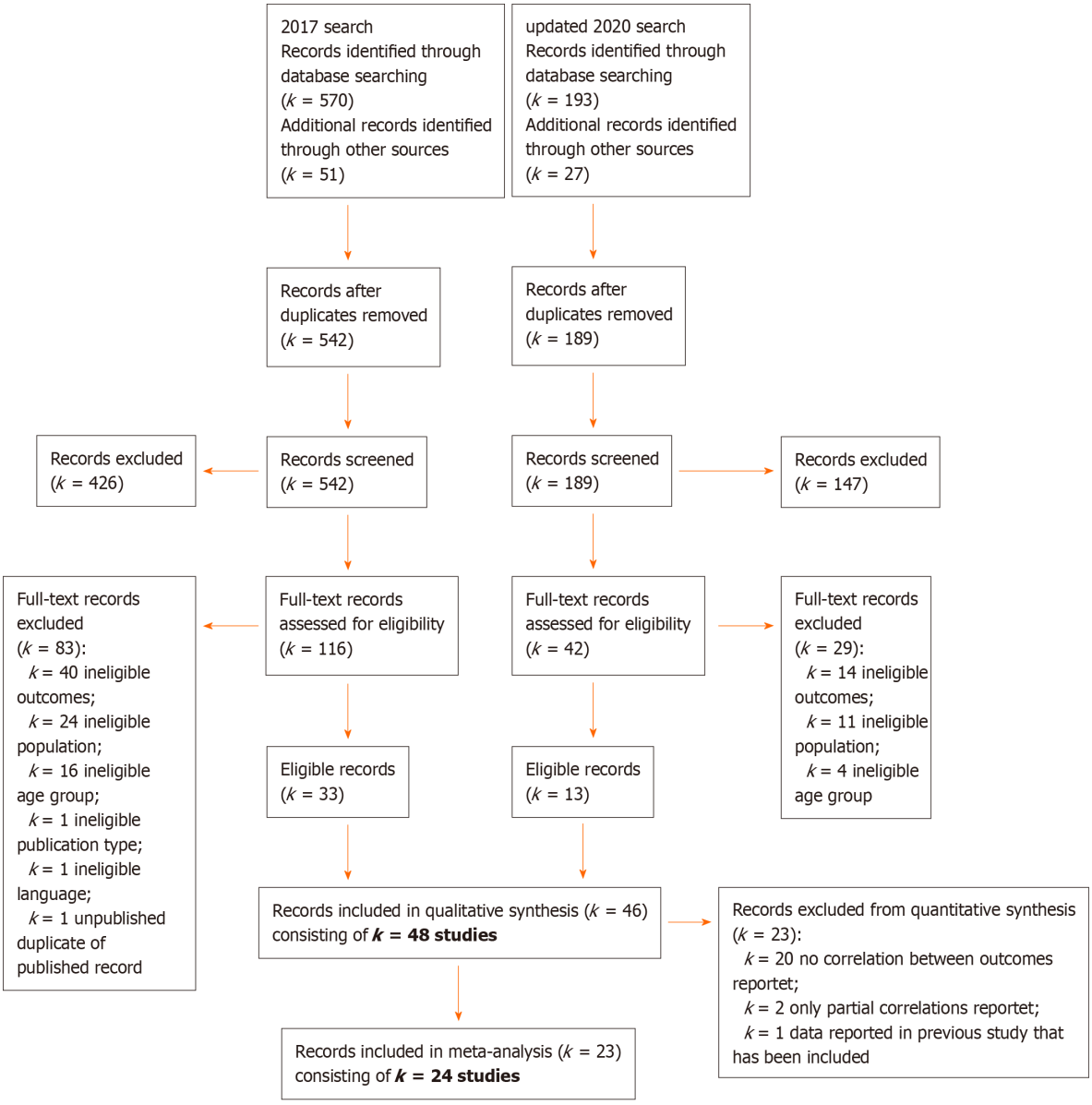


Figure 1 Adapted PRISMA Flowchart for study selection in this systematic review and meta-analysis.

RESULTS

Study selection

Figure 1 shows this review's selection process divided into the first search in 2017 and the search updated in 2020. Overall, k = 763 records were identified through database searching. A total of k = 78 additional records were identified through other sources. Initially, a total of k = 110 duplicates were removed. Next, the first author screened the titles and abstracts of the identified studies. k = 158 records remained in the selection process after screening. Overall, k = 46 records fulfilled our inclusion criteria. Of those, each of two records reported two studies[23,49], resulting in k = 48 studies overall included in this systematic literature review. In two cases, working groups analyzed the same datasets in two independently published records[27,28,50,51]. For quantitative synthesis, k = 24 studies fulfilled our inclusion criteria and were included in meta-analysis.

Characteristics of studies included in this systematic review

An overview of the included studies and study characteristics is found in Table 1. They contain k = 47 published studies carried out in Australia, Canada, Denmark, Germany, Italy, Iran, Turkey, the United Kingdom or Ireland, and United States between 2003 and 2020. The k = 1 remaining study is characterized as gray literature and was submitted in 2014 to qualify for a doctorate degree at a German university.

Table 1 Overview of studies included in the systematic review

Ref.	Sample	*n*	Female (%)	Age in year (range), mean ± SD	Risk of bias	POS/NEG/meta-worry	Worry	Anxiety
Babaei *et al*[55]	NC	200	NA	NA	Mod (9)	MCQ-30	-	GHQ-scale
Bacow *et al*[27]	Total/C[1,2,3,4]/NC	98/78/20	NA/63%/65%	(7-17) NA/(NA) 11.9 ± 3.1/(NA) 12.4 ± 3.0	Low (14)	MCQ-C	ADIS-C-section	ADIS-C/P
Bacow *et al*[28]	Total/C[1,2,3,4]/NC	98/78/20	NA/63%/65%	(7-17) NA/(NA) 11.9 ± 3.1/(NA) 12.4 ± 3.0	Low (14)	MCQ-C	PSWQ-C; ADIS-C-section	ADIS-C/P
Benedetto *et al*[64]	NC	184	53%	(11-13) 12.0 ± 0.9	Mod (13)	MCQ-C	PSWQ-C	RCMAS-2
Benedetto *et al*[49], study1	NC	191	49%	(13-18) 16.4 ± 1.76[a]	Mod (13)	MCQ-C	-	RCMAS-2
Benedetto *et al*[49], study2	C[1,5]/NC[b]	14/14	57%/NA	(12-17) 14.9 ± 1.6/NA	Low (14)	MCQ-C	-	RCMAS-2
Boysan *et al*[92]	NC	805	49%	(11-17) 13.9 ± 1.4	Low (14)	MCQ-C	-	STAI-C
Carr and Szabó[72]	NC	93	48%	(7-12) 10.0 ± 1.2	Low (16)	MCQ-C	CAWS	-
Cartwright-Hatton *et al*[53]	C[6]/NC	(11)/166	(64%)/66%	NA/(13-17) 15.3 ± NA	Mod (12)	MCQ-A	-	RCMAS
Donovan *et al*[80]	Total/C[1]/NC	50/25/25	60%/NA/NA	(7-12) 9.9 ± 1.5/NA/NA	Low (14)	MCQ-C	PSWQ-C	ADIS-C
Donovan *et al*[65]	NC	114	51%	(8-12) 9.9 ± 1.3	Low (15)	MCQ-C	PSWQ-C	-
Ellis and Hudson[24]	Total/C[1,5]/NC	123/81/42	NA/57%/52%	(12-17) NA/(NA) 14.1 ± 1.5/(NA) 13.7 ± 1.4	Low (15)	MCQ-A	PSWQ	ADIS-C/P; SCAS-C/P
Esbjørn *et al*[23], study1	NC	587	55%	(9-17) 12.5 ± 0.9[a]	Mod (12)	MCQ-C_{30}	PSWQ-C	SCARED-R
Esbjørn *et al*[23], study2	Total/C[1,4,7,3]/NC	93/50/43	NA/NA/NA	(7-12) 9.8 ± 1.6/NA/NA	Mod (13)	MCQ-C_{30}	-	ADIS-C/P
Esbjørn *et al*[93]	NC	111	64%	(8-12) 10.1 ± 1.4	Low (15)	MCQ-C_{30}	PSWQ-C	ADIS-C/P; RCADS
Esbjørn *et al*[66]	NC	974	55%	(9-17)	Low (15)	MCQ-C_{30}	PSWQ-C	SCARED-R
Esbjørn *et al*[56]	C[1]	44	50%	(7-13) 9.7 ± 1.6	Low (15)	MCQ-C_{30}	PSWQ-C	ADIS; RCADS
Fergus and Limbers[57]	NC (TG)/NC (CG)	39/34	62%/71%	(NA) 13.8 ± 0.5/(NA) 13.8 ± 0.7	Low (17)	MCQ-C	-	CTAS
Fisak *et al*[73]	NC	175	66%	(11-18) 13.9 ± 1.5	Mod (12)	MCQ-C;MWQ	PSWQ-C	-
Francis *et al*[50]	NC	312	55%	(9-15) 11.9 ± 1.2	Low (15)	MCQ-C	PSWQ-C	SCAS;MASC
Francis *et al*[51]	NC	312	55%	(9-15) 11.9 ± 1.2	Mod (14)	MCQ-C	PSWQ-C	-
Gallagher and Cartwright-Hatton[94]	NC	168	85%	(16-18) 17.2 ± 0.9	Mod (11)	MCQ-30	-	STAI-T
Gini *et al*[67]	NC	1169	48%	(14-17) 15.8 ± 1.1	Mod (11)	MCQ-30	PSWQ-C	GAD7
Hearn *et al*[25]	C[3]	126	60%	(8-17) 11.3 ± 2.7	Mod (13)	MCQ-C	PSWQ-C(SF)	ADIS;SPAI-10-C/P

Hearn *et al*[74]	Total/C[1,3]/NC	60/40/20	70%/NA/NA	(8-12) 9.9 ± 1.3/NA/NA	Low (15)	MCQ-C	PSWQ-C(SF)	ADIS; SCAS
Hearn *et al*[26]	Total/C[3] (TG)/C[3] (WL)	125/95/30	60%/NA/NA	(8-17) 11.3 ± 2.7/NA/NA	Low (17)	MCQ-C	PSWQ-C(SF)	ADIS; SPAI-10
Holmes *et al*[59]	C[1]	1	0%	10	Low (16)	MCQ-C	PSWQ-C	ADIS-C/P;SCAS-C/P
Holmes *et al*[58]	Total/C[1] (TG)/C[1] (WL)	42/20/22	67%/NA/NA	(7-12) 9.6 ± 1.4/NA/NA	Low (17)	MCQ-C	PSWQ-C	ADIS-C/P;SCAS-C/P
Irak[78]	NC	470	44%	(8-17) 12.2 ± 2.8	Mod (12)	MCQ-C	-	STAI-C
Kertz and Woodruff-Borden [75]	NC	80	71%	(8-12) 9.6 ± 1.1	Mod (12)	MCQ-C	PSWQ-C(SF)	RCMAS
Laugesen *et al*[71]	NC	528	49%	(14-18) 15.6 ± 0.9	Low (15)	WW-II	PSWQ-C	WAQ
Lønfeldt *et al*[76]	NC	188	66%	(7-12) 10.0 ± 1.4	Low (14)	MCQ-C_{30}	-	ADIS-P; RCADS
Lønfeldt *et al*[77]	NC	1062	55%	(9-17) 12.3 ± 1.7	Low (14)	MCQ-C_{30}	-	SCARED-R
Mather and Cartwright-Hatton[95]	NC	166	66%	(13-17) 15.1 ± 1.4	Mod (12)	MCQ-A	-	RCMAS
Matthews *et al* [81]	NC	223	56%	(13-16) NA	Mod (13)	MCQ-A	-	-
Naumann[68]	NC	972	52%	(7-14) 10.6 ± 1.5	Low (14)	MKF-K	PSWQ-C	SCAS
Normann *et al*[60]	C[1,4,3,7]	44	50%	(7-12) 9.9 ± 1.6	Low (14)	MCQ-C_{30}	-	ADIS-C/P; SCARED-R
Reinholdt-Dunne *et al*[79]	C[1,4,3,7]/NC	169/182	53%/55%	(7-14) 9.9 ± 1.8/(7-12) 10.0 ± 1.4	Low (16)	MCQ-C_{30}	-	RCADS
Sanger and Dorjee[61]	NC (TG)/NC (CG)	20/25	50%/68%	(16-18) 16.6 ± 0.6/(16-18) 17.1 ± 0.6	Mod (12)	MCQ-A	-	-
Simons and Vloet [62]	C[7]	3	100%	(14-17) 15.3 ± 1.5	Mod (13)	MCQ-A	SCAS-scale	SCAS
Smith and Hudson[52]	Total/C[1,3,2,7,4,8]/NC	83/49/34	60%/NA/NA	(7-12) 9.2 ± 1.6/NA/NA	Mod (13)	MCQ-C	-	ADIS-C/P; SCAS
Thorslund *et al* [63]	C[1,3,9]	10	70%	(14-17) 15.2 ± NA	Low (14)	MCQ-C	PSWQ-C	MINIKid
White and Hudson[30]	NC	187	31%	(7-12) 10.6 ± 1.7	Low (15)	MCQ-CR	PSWQ-C	SCAS
Wilson *et al*[82]	NC	72	54%	(11-16) 13.2 ± 1.0	Mod (13)	MCQ-A	PSWQ-C	MASC
Wilson and Hall [69]	NC	151	56%	(13-16) 15.1 ± 1.0	Mod (12)	MCQ-A	TCQ-scale	-
Wilson and Hughes[70]	NC	57	61%	(6-10) NA	Mod (12)	Interview	PSWQ-C	MASC
Yavuz *et al*[96]	NC	1817	54%	(14-17) 15.4 ± 1.1	Mod (12)	MCQ-C	-	NMP-Q
Zimmermann *et al*[54]	NC	221	55%	(13-17) 14.9 ± 1.4	Mod (12)	MCQ-A	-	SBB-ANZ

[a]Mean was only reported for subsamples and has been weighted on sample size.
[b]Subsample from study 1.
Superscript numbers show diagnosis of clinical groups in descending order:

[1]Generalized Anxiety disorder.
[2]Obsessive-compulsive-disorder.
[3]Social Anxiety Disorder.
[4]Separation Anxiety disorder.
[5]Other Anxiety disorder.
[6]Any emotional disorder.
[7]Specific Phobia.
[8]Post-traumatic stress disorder.
[9]Panic disorder/agora phobia.

NA: Not available; TG: Treatment group; WL: Waiting list; CG: Control group; POS: Positive beliefs about worry; NEG: Negative beliefs about worry; Mod: Moderate; MCQ-30: Metacognitions Questionaire-30-Item Version; MCQ-C: Metacognitions Questionnaire for children; MCQ-A: Metacognitions Questionnaire-Adolescent Version; MKF-K: Metakognitions-Fragebogen für Kinder; MCQ-CR: Revised Metacognitions Questionnaire for Children; MCQ-$C_{30:}$ Metacognitions Questionnaire for Children–30Item Version; MWQ: Meta-Worry Questionnaire; ADIS-C/P: Anxiety Disorders Interview Schedule Child/Parent Versions; PSWQ: Penn State Worry Questionnaire; PSWQ-C: Penn State Worry Questionnaire for Children; WAQ: Worry and Anxiety Questionnaire; RCMAS,RCMAS-2: Revised Children's Manifest Anxiety Scale; STAI-C: State-Trait Anxiety Inventory for Children; CAWS: Child and Adolescent Worry Scale; SCAS: Spence Children's Anxiety Scale; SCARED-R: Revised Version of the Screen for Child Anxiety Related Emotional Disorders; MASC: Multidimensional Anxiety Scale for Children; GHQ: General Health Questionnaire; TCQ: Thought Control Questionnaire; SPAI-10: Social Phobia and Anxiety Inventory for Children; CTAS: Children´s Test Anxiety Scale; MINI Kid: Mini International Neuropsychiatric Interview for Children and Adolescents; GAD7: 7-item Generalized Anxiety Disorder scale; NMP-Q: Nomophobia Questionnaire; SBB-ANZ: Diagnostik-System für Psychische Störungen nach ICD-10 und DSM-IV für Kinder und Jugendliche – Selbstbeurteilungsfragebogen Angst- und Zwangsstörungen; SD: Standard deviation.

A total of n = 12839 participants were examined in the included studies. Median sample size was n = 138.50 per study, range n = 1 to n = 1817. Gender distribution was reported in k = 46 studies. Overall, a mean of 56.84% of participants per study described themselves as female, ranging from 0% to 100% per study. The age of participants ranged from 6 to 18 years. k = 30 studies involved a non-clinical sample, k = 8 studies involved a purely clinical sample, and k = 10 studies included both a clinical group and a non-clinical group. The non-clinical samples were usually convenience samples recruited from schools. Studies with clinical samples included the primary diagnoses GAD, SAD, SoD, panic disorder/agoraphobia, and specific phobia. In three studies, OCD or post-traumatic stress disorder were classified as anxiety disorders[27,28,52]. Patients with these primary disorders represented a percentage of 8.1% to 18.4% of patients included with anxiety disorders. Most studies revealed a cross-sectional design. Three studies included a retest-measurement to assess test-retest correlations for validating different questionnaires[53-55]. Nine studies followed a longitudinal design in the form of intervention studies with pre-post- (and follow-up) measurement points[26,56-63].

Risk of bias

We used the AXIS-tool to assess the risk of bias. Most of the studies were classified as low risk of bias (k = 25) and moderate risk of bias (k = 23), whereas no study was classified as having a high risk of bias (see Table 1).

What evidence is there for positive relationships between POS, NEG, and meta-worry with each other, worry, and anxiety for children and adolescents?

Relationships between POS, NEG, meta-worry, and worry: Table 2 provides an overview of the relationships reported in the included studies. In total, k = 18 studies researched the relationships between POS, NEG, and worry. Most thereof demonstrated correlations between worry and both POS and NEG[24,51,64-70]. Moreover, two studies collected POS exclusively and reported significant correlations between worry and POS[71,72]. Two studies showed that POS and NEG contribute to worry as unique predictors[23,73], and another study that exclusively measured POS identified it as a unique predictor of worry[72]. However, other studies found that worry correlated only with NEG, not with POS[26,30,74,75]. Another study detected a correlation between POS and worry that disappeared after the authors controlled for worry contents, while worry nevertheless continued to correlate with NEG[28]. One study detected no group differences in worry between participants who described POS or NEG verbally in open-ended questions and those who did not[70]. Only one study investigated the relationship between meta-worry and worry and observed positive correlations between them[73].

Results of meta-analysis: Table 3 shows our meta-analysis results. Meta-analysis (k = 13) for correlation between POS and worry resulted in an overall small to medium effect size [r = 0.27 (0.22, 0.33), P < 0.001]. Q-Test for heterogeneity was significant (Q =

Table 2 Extracted correlational coefficient on measures of positive beliefs about worry/negative beliefs about worry and worry/anxiety

Ref.	Worry		Anxiety		POS	Age	
	POS	NEG	POS	NEG	NEG	POS	NEG
Babaei *et al*[55]	-	-	-0.053	-0.303[b]	0.21[b]	-	-
Bacow *et al*[27]	-	-	-	-	-	NA	NA
Bacow *et al*[28]	0.21[a]	0.55[b]	-	-	-	-	-
Benedetto *et al*[64]	0.23[b]	0.70[b]	0.29[b]	0.65[b]	0.30[b]		
Benedetto *et al*[49], study1	-	-	0.20[3,a]; 0.01[4]	0.56[3,b]; 0.48[4,b]	0.17[3]; 0.31[4,b]	-	-
Benedetto *et al*[49], study2	-	-	-0.68[1,a]; 0.38[2]	0.56[1,a]; 0.42[2]	-0.41[1]; 0.69[2,b]	-	-
Boysan *et al*[92]	-	-	-	-	-	-	-
Carr and Szabó[72]	0.35[c]	-	-	-	-	0.02	-
Cartwright-Hatton *et al*[53]	-	-	0.32[c]	0.67[c]	-	-	-
Donovan *et al*[80]	-	-	-	-	-	-	-
Donovan *et al*[65]	0.22[a]	0.72[b]	-	-	0.20[a]	-	-
Ellis and Hudson[24]	0.49[b]	0.84[b]	0.46[b]	0.72[b]	-	0.16	0.16
Esbjørn *et al*[23], study1	-	-	-	-	-	-	-
Esbjørn *et al*[23], study2	-	-	-	-	-	-	-
Esbjørn *et al*[93]	-	-	-	-	-	-	-
Esbjørn *et al*[66]	0.25[c]	0.31[c]	0.17[c]	0.55[c]	0.25[c]	-	-
Esbjørn *et al*[56]	-	-	-	-	-	-	-
Fergus and Limbers[57]	-	-	-	-	-	-	-
Fisak *et al*[73]	-	-	-	-	-	-	-
Francis *et al*[50]	-	-	-	-	-	-	-
Francis *et al*[51]	0.39[b]	0.69[b]	-	-	0.31[b]	-	-
Gallagher and Cartwright-Hatton[94]			-	-	-	-	-
Gini *et al*[67]	0.32[c]	0.65[c]	0.22[c]	0.60[c]	0.16[c]	-	-
Hearn *et al*[25]	0.16	0.50[b]	0.02	0.39[b]	0.08	-	-
Hearn *et al*[74]	-	-	-	-	-	-	-
Hearn *et al*[26]	0.02	0.48[b]	0.01	0.36[b]	-	-	-
Holmes *et al*[59]	-	-	-	-	-	-	-
Holmes *et al*[58]	-	-	-	-	-	-	-
Irak[78]	-	-	0.194[c]	0.412[c]	-	-	-
Kertz and Woodruff-Borden[75]	0.14 (P)	0.53[c] (P)	-	-	-	-	-
Laugesen *et al*[71]	0.37[c] (P)	-	-	-	-	-	-
Lønfeldt *et al*[76]	-	-	0.31[b]	0.57[b]	0.30[b]	0.10	0.06
Lønfeldt *et al*[77]	-	-	0.19[a]	0.58[a]	0.23[c]	-0.01	-0.08[a]
Mather and Cartwright-Hatton[95]	-	-	-	-	-	-	-
Matthews *et al*[81]	-	-	-	-	0.47[a]	-0.05	-0.18[b]
Naumann[68]	0.20[b]	0.63[b]	0.20[b]	0.55[b]	0.07	-	-
Normann *et al*[60]	-	-	-	-	-	-	-
Reinholdt-Dunne *et al*[79]	-	-	0.09[1]; 0.36[2,b]	0.62[1,b]; 0.68[2,b]	0.05[1]; 0.29[2,b]	0.10[1]; -0.10[2]	0[1]; 0[2]
Sanger and Dorjee[61]	-	-	-	-	-	-	-
Simons and Vloet[62]	-	-	-	-	-	-	-

Smith and Hudson[52]	-	-	0.30[b]	0.47[b]	0.36[b]	-	-
Thorslund *et al*[63]	-	-	-	-	-	-	-
White and Hudson[30]	0.08	0.65[b]	0.20[b]	0.56[b]	0.27[a]	0.06	0.07
Wilson *et al*[82]	0.35[b]	0.74[b]	0.19	0.51[a]	NA	< 0.16	< 0.16
Wilson and Hall[69]	0.33[c]	0.51[c]	-	-	0.29[c]	-	-
Wilson and Hughes[70]	-	-	-	-	-	-	-
Yavuz *et al*[96]	-	-	-	-	-	-	-
Zimmermann *et al*[54]	-	-	0.22[b]	0.57[b]	-	0.16[a]	0.12

[1]Clinical group.
[2]Non-clinical group.
[3]Female subsample.
[4]Male subsample.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
NA: Not available; POS: Positive beliefs about worry; NEG: Negative beliefs about worry; (P): Partial correlation.

Table 3 Summary of results for random effect models for meta-analysis on correlational coefficient on measures of positive beliefs about worry/negative beliefs about worry and worry/anxiety

	Overall effect							Heterogenity test		
Meta-analysis	***k***	***r***	**95%CI, *r***	**95%PI, *r***	**Fisher's z**	**95%CI, z**	**Z**	**Q**	**I^2**	**T^2**
POS and worry	13	0.27	(0.22, 0.33)	(0.08, 0.45)	0.28	(0.22, 0.34)	9.56, $P <$ 0.001	36.14, $P < 0.001$	67 %	0.01
NEG and worry	12	0.64	(0.55, 0.72)	(0.27, 1.25)	0.76	(0.62, 0.90)	10.49, $P <$ 0.001	233.90, $P < 0.001$	95 %	0.06
POS and anxiety	18	0.20	(0.16, 0.25)	(0.00, 0.38)	0.20	(0.16, 0.25)	8.54, $P <$ 0.001	52.11, $P < 0.001$	67 %	0.01
NEG and anxiety	18	0.53	(0.46, 0.60)	(0.19, 0.76)	0.59	(0.50, 0.69)	12.32, $P <$ 0.001	234.07, $P < 0.001$	93 %	0.04
POS and NEG	17	0.24	(0.18, 0.28)	(0.04, 0.41)	0.24	(0.18, 0.29)	8.49, $P <$ 0.001	66.44, $P < 0.001$	76 %	0.01

k: Number of studies included in meta-analysis; *r*: Pearson's product-moment correlation; CI: Confidence interval; PI: Prediction interval; SE: Standard error; POS: Positive beliefs about worry; NEG: Negative beliefs about worry.

36.14, $P < 0.001$), and inconsistency can be described as moderate to high ($I^2 = 67\%$). For correlation between NEG and worry ($k = 12$), the overall correlation coefficient was $r = 0.64$ (0.55, 0.72), $P < 0.001$, indicating a large effect. Heterogeneity tests resulted in significant and substantial inconsistency: $I^2 = 95\%$, $Q = 233.90$, $P < 0.001$. Forest plots for meta-analysis are depicted in Figures 2 and 3. As only one study examined meta-worry[73], we could not conduct a meta-analysis for a correlation with worry.

Relationships between POS, NEG, meta-worry, and anxiety: $k = 21$ studies analyzed the association between POS and NEG and anxiety symptoms. Correlations between POS, NEG, and anxiety were demonstrated in the majority of studies[24,30,52-54,64,66-68,76-78]. However, other study findings contradict those results. Three studies revealed correlations between anxiety and NEG, while anxiety failed to correlate with POS[25,26,70]. NEG contributed to anxiety as a unique predictor in one study, while POS did not predict anxiety significantly[23]. In study 1 by Benedetto *et al*[49], anxiety did correlate with NEG in female and male participants, whereas POS and anxiety correlated significantly in female subjects only. In study 2, those two correlations were proven in adolescents with an anxiety disorder only but not in a non-clinical sample [49]. Another study showed that NEG correlated with anxiety in clinical and non-clinical groups, while POS were only associated with anxiety in a clinical group[79]. In the study by Wilson and Hughes[70], children's anxiety scores did not differ as to

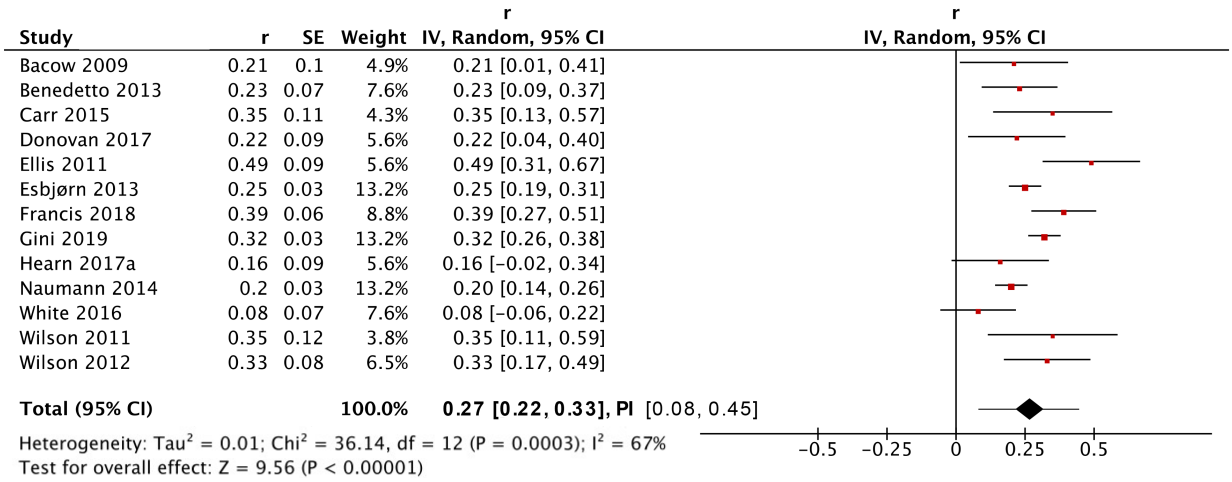


Figure 2 Meta-analysis forest plot on the correlation between measures of positive metacognitive beliefs about worry and worry. CI: Confidence interval; SE: Standard error.

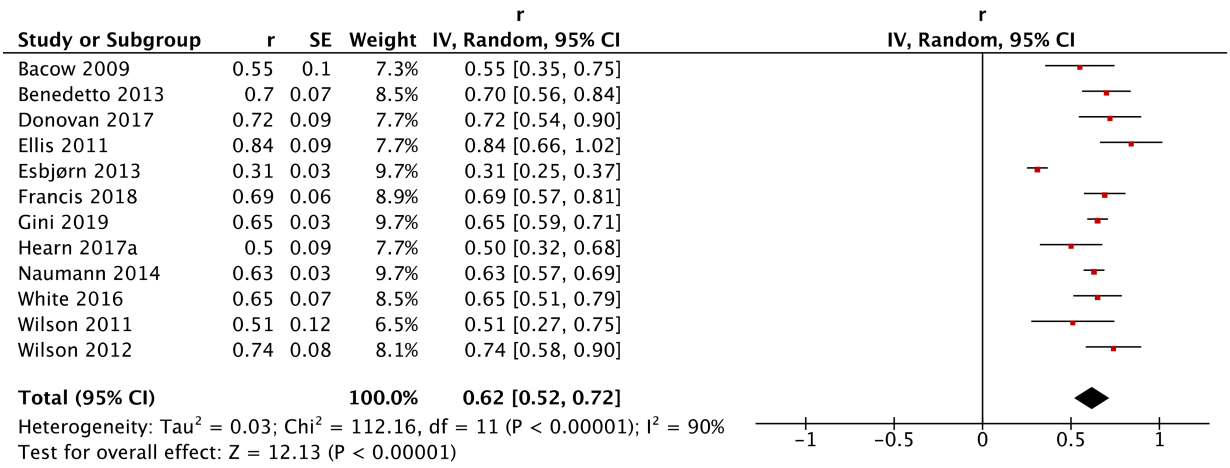


Figure 3 Meta-analysis forest plot on the correlation between measures of negative metacognitive beliefs about worry and worry. CI: Confidence interval; SE: Standard error.

whether they reported NEG or POS. One study even identified a negative correlation between NEG and anxiety, while POS did not correlate with anxiety[55]. No study examined whether meta-worry was related to anxiety. Extracted relationships are shown in Table 2.

Results of meta-analysis: For the correlation between POS and anxiety, we identified k = 18 studies for meta-analysis. The overall effect size was small [r = 0.20, 95%CI (0.16, 0.25), P < 0.001]. Q-Test for heterogeneity was significant (Q = 52.11, P < 0.001) and the amount of inconsistency is moderate to high (I^2 = 67%). Testing of overall-effect size when correlating NEG and anxiety (k = 18) resulted in a large effect [r = 0.53 (0.46, 0.60), P < 0.001]. With respect to heterogeneity, the Q-statistic is significant (Q = 234.07, P < 0.001), and results speak for inconsistency (I^2 = 93%). Our meta-analysis results are displayed in Table 3, the forest plots in Figures 4 and 5. No meta-analyses for correlations between worry and meta-worry were possible as no study investigated potential relationships between those variables.

Clinical *vs* non-clinical groups: A total of k = 10 studies included both clinical and non-clinical samples. Three studies showed that their clinical sample held significantly higher POS and NEG than the non-clinical group[24,52,79]. In other studies, clinical participants reported more NEG than non-clinical participants, POS revealed no group difference[49,53,74,80]. One study found that both investigated clinical samples (GAD, other anxiety disorders) held significant higher NEG than a non-clinical group, but only patients with GAD differed from healthy controls in case of POS[23]. Two studies

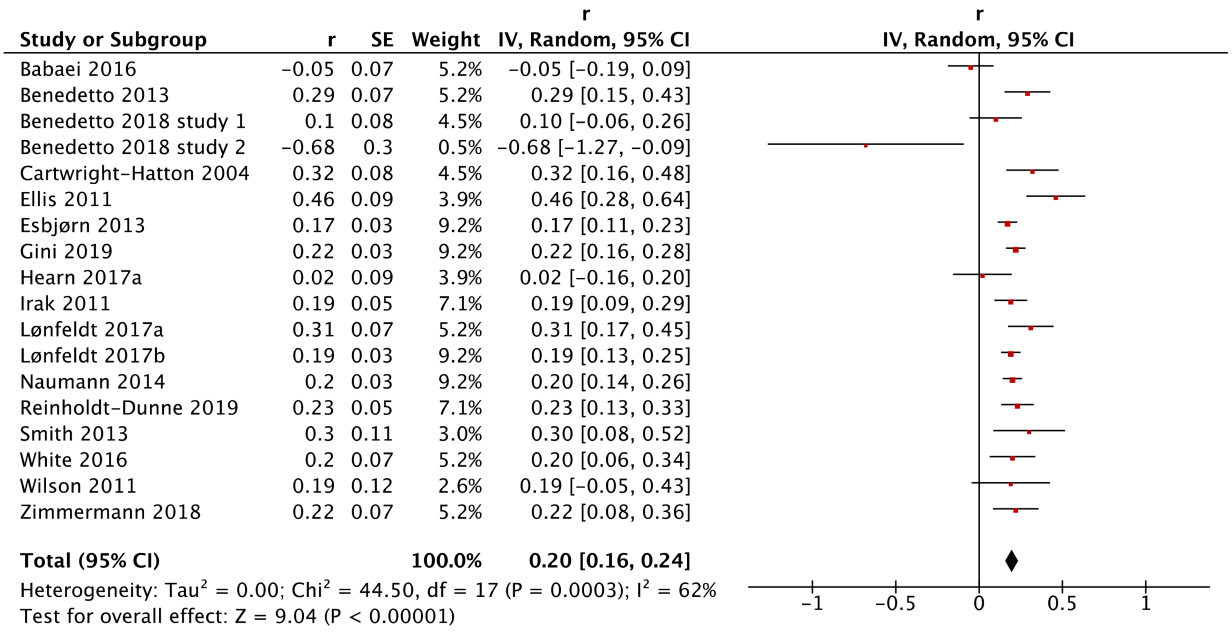


Figure 4 Meta-analysis forest plot on the correlation between measures of positive metacognitive beliefs about worry and anxiety. CI: Confidence interval; SE: Standard error.

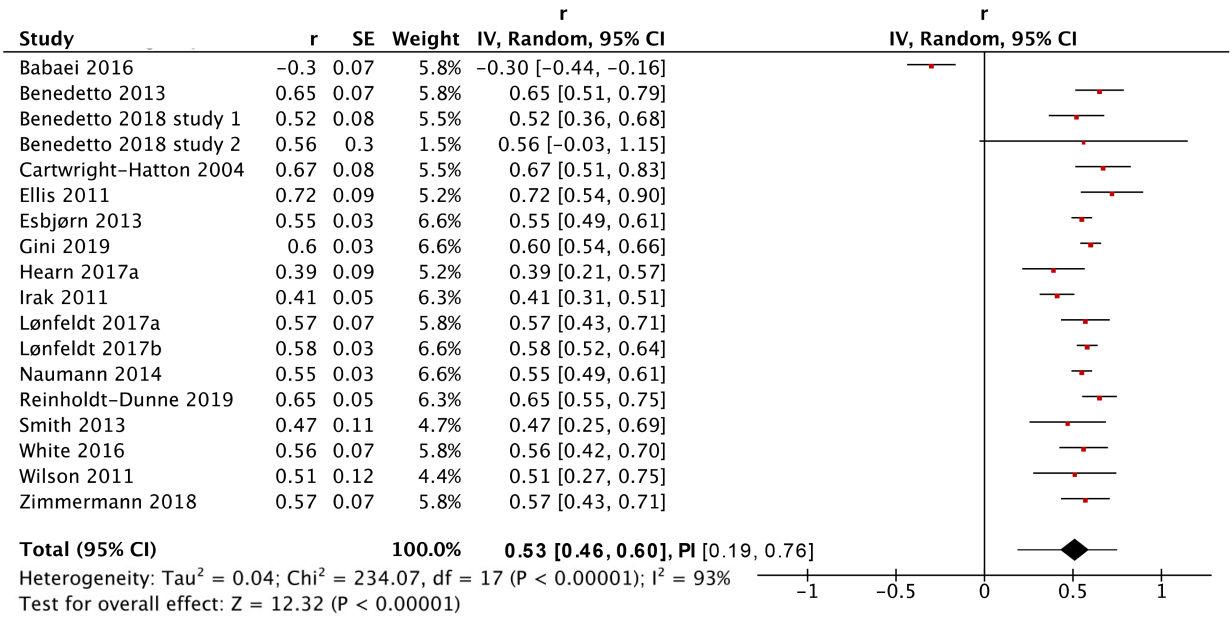


Figure 5 Meta-analysis forest plot on the correlation between measures of negative metacognitive beliefs about worry and anxiety. CI: Confidence interval; SE: Standard error.

failed to demonstrate significant differences between a non-clinical sample and patients with anxiety disorders for POS or NEG[27,28]. Furthermore, k = 4 studies compared different anxiety disorders with each another specifically. The findings by Bacow *et al*[27] indicate that children and adolescents with OCD, SAD, SoD, and non-clinical controls do not differ in POS or NEG. Another study reported no group differences between patients with GAD and patients with SoD for POS or NEG[74]. Ellis and Hudson[24] detected no differences either between their sample with GAD and one with other anxiety disorders. Nevertheless, in their study 2, Esbjørn *et al*[23] demonstrated that patients with GAD had higher NEG than those with other anxiety disorders, whereas POS did not differ between groups.

Relationships between POS, NEG, and meta-worry: Correlations between POS and NEG were explored in k = 19 studies, as shown in Table 2. Most studies identified a

positive correlation between POS and NEG[30,51,52,55,64-67,69,76,77,81]. In Benedetto *et al*[49] study 1, POS and NEG correlated positively with each other for male but not female participants. In their second study, a correlation between POS and NEG only became evident in a non-clinical sample, not a clinical one. Reinholdt-Dunne *et al*[79] reported the same result. Still other working groups failed to demonstrate any significant correlation between POS and NEG[25,26,68,82], and none analyzed relationships between POS and NEG with meta-worry.

Results of meta-analysis: We excluded one study from meta-analysis that showed a correlation between POS and NEG since they reported no effect size for correlation [82]. Overall effect size for the POS with NEG correlation (k = 17) was small to medium, r = 0.24 (0.18, 0.28), P < 0.001. Heterogeneity was shown to be significant (Q = 66.44, P < 0.001), and inconsistency was high (I^2 = 76%). Results are displayed in Table 3 and Figure 6.

At what age do children report POS, NEG, and meta-worry, and does age play a role in relationships with worry and anxiety?

Onset of metacognitive beliefs about worry: k = 31 studies examined metacognitive beliefs in children under the age of 12 years, and k = 14 studies included populations from age 7 years upwards. Only one study investigated metacognition in children as young as six[70]. Those authors asked children between 6 and 10 years of age to fill out open-ended questions about POS and NEG. Fifty-six percent of children expressed one or more POS, and 77% of children expressed one or more NEG; they observed no age-related differences in the numbers who named POS or NEG[70]. Six-year-old children thus do not seem to differ from older children in their POS and NEG. Other studies analyzed how well young children understand metacognitive questionnaires. Smith and Hudson[52] found that six items on the often used Metacognitions Questionnaire for Children[28] were not adequately understood by 35.8% to 78.6% of the 7- and 8-year-olds they investigated. White and Hudson[30] changed those six items and included a fifth answer option, "I don't understand". Their new instrument, the Revised Metacognitions Questionnaire for Children[30], was tested in a sample of 187 7- to 12-year-old children. No item, including the six newly changed items, was marked as "I don't understand" by more than 25% of 7-year-olds and 17% of 8-year-olds, indicating that the vast majority of this age group (75%-83%) was indeed able to rate their POS and NEG[30]. A small negative correlation was found between age and the number of not-understood items, and a similar significant group difference between 7- to 8-year-olds and 9- to 12-year-olds appeared, indicating that children understand POS and NEG better as they age[30].

Relationship between age and metacognition about worry: Table 2 contains an overview of extracted relationships. Of all included studies, only a minority investigated whether metacognitive beliefs change with age (k = 12). Most of those studies did not detect any correlation between POS and NEG, neither with participants' age nor age-related differences[24,27,28,30,72,77,79,82]. In the open-ended questions asked verbally by Wilson and Hughes[70], 56% of children claimed to have at least one POS and 77% at least one NEG. The authors revealed no age-related difference in these answers from children aged 6 to 10 years. In contrast, another study's results suggest that NEG may decline with age, as age did not correlate with POS, but NEG did correlate with age (with a small negative effect[76]). Interestingly, another study identified a small positive correlation between POS and age, but no significant correlation between NEG and age[54]. Another study also demonstrated a significant age effect for POS but none for NEG[78].

Results of meta-regressions with age as covariate: Results of the meta-regressions with mean age as covariate are presented in Table 4. Z-tests for latitudes did not reach significance in any meta-regression, therefore the null hypothesis of no effect cannot be rejected. We therefore found that mean age was not a significant covariate in any of the tested correlations.

Which methods are currently applicable to assess POS, NEG, and meta-worry in childhood and youth?

In total, the authors administered six different questionnaires to assess POS and NEG together. These include the Metacognitions Questionnaire-30-Item Version (MCQ-30) [83], MCQ - Adolescent Version[53], and MCQ for Children (MCQ-C)[28]. The Revised MCQ for Children (MCQ-CR)[30], MCQ for Children-30-Item version (MCQ-C_{30})[66],

Table 4 Results of meta-regressions on correlational coefficient on measures of positive beliefs about worry/negative beliefs about worry and worry/anxiety with mean age as covariate

Meta-regression		*B*	*SEB*	95%lower	95% upper	*Z*	*P*
POS and	Intercept	0.5082	0.356	-0.254	1.271	1.429	0.175
Anxiety[1]	Latitude	-0.0265	0.028	-0.086	0.033	-0.958	0.354
POS and	Intercept	-0.0905	0.195	-0.525	0.344	-0.464	0.652
Worry[2]	Latitude	0.0302	0.016	-0.005	0.065	1.911	0.085
NEG and	Intercept	0.4427	0.128	0.168	0.718	3.450	0.004[b]
Anxiety[3]	Latitude	0.0094	0.010	-0.012	0.031	0.940	0.363
NEG and	Intercept	0.6482	0.225	0.139	1.157	2.881	0.018[a]
Worry[4]	Latitude	0.0004	0.018	-0.040	0.041	0.021	0.984
POS and	Intercept	0.5256	0.260	-0.042	1.093	2.019	0.066
NEG[5]	Latitude	-0.0286	0.021	-0.074	0.017	-1.357	0.200

[1]Based on *k*: 16 studies.
k: 2 studies[55,67] were excluded as no mean age was reported;
[2]Based on *k*: 12 studies.
k: 1 study[67] was excluded as no mean age was reported;
[3]Based on *k*: 16 studies.
k: 2 studies[55,67] were excluded as no mean age was reported;
[4]Based on *k*: 11 studies.
k: 1 study[67] was excluded as no mean age was reported;
[5]Based on *k*: 14 studies.
k: 3 studies[55,67,81] were excluded as no mean age was reported.
[a]$P < 0.05$.
[b]$P < 0.01$.
B: Point estimate; *SEB*: Standard error of point estimate; POS: Positive metacognitive beliefs about worry; NEG: Negative metacognitive beliefs about worry.

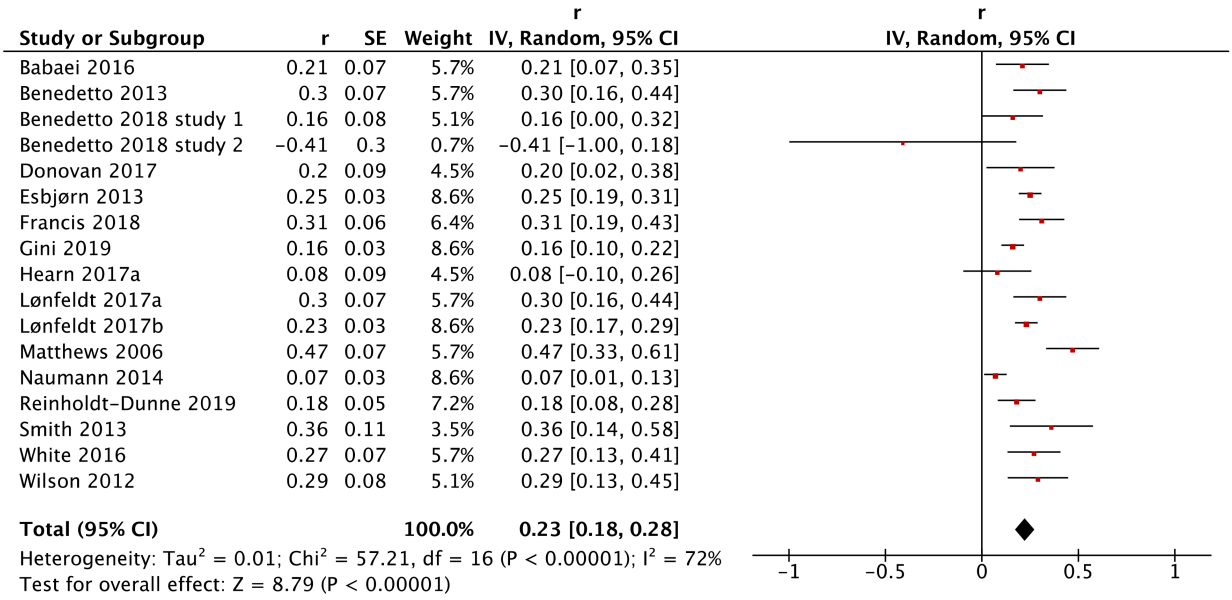


Figure 6 Meta-analysis forest plot on the correlation between measures of positive metacognitive beliefs about worry and negative metacognitive beliefs about worry. CI: Confidence interval; SE: Standard error.

and Metakognitionsfragebogen für Kinder[68] are more recent adaptations. All those questionnaires are variations of the MCQ developed by Cartwright-Hatton and Wells [22]. Despite POS and NEG, it also covers cognitive confidence, the need for control, and cognitive self-consciousness[22]. Furthermore, with Why Worry-II[84], we

extracted one questionnaire that exclusively measures POS. Only one study assessed meta-worry[73]. Its authors administered the meta-worry questionnaire[21] for this purpose.

Of the studies included, only one assessed POS and NEG in children as young as 6 years of age[70]. Due to the lack of reading skills at this age, the children were orally asked these open-ended questions: "Worry can sometimes be helpful and good. Tell me some reasons why worry is good" and "Worry can sometimes be unhelpful and bad. Tell me some reasons why worry is bad"[70]. The authors assigned the children's responses to the categories POS (*e.g.*, solves problems, motivates you, keeps you safe) and NEG (*e.g.*, impacts on activity, is uncontrollable, makes you unwell). An overview of the measurements used in these studies is found in Table 5.

DISCUSSION

To the best of our knowledge, this review is the first to describe systematically measuring instruments for POS and NEG as well as results on the validity of the metacognitive model by meta-analysis on correlations between POS and NEG with each other, worry, and anxiety. Presenting 48 studies, we provide a broad overview of this topic, upon which future research can build. We conducted a consensus rating of 20.89% of full-texts with agreement in 90.32%. Good interrater agreement was attained regarding the risk of bias assessment. No study was rated as showing a high risk of bias. Data from 24 studies could be included in quantitative synthesis to meta-analyze the strength of effect sizes. We were also able to analyze mean age as a moderator in meta-regressions and identify various measurement instruments for different age ranges and newer adaptations like MCQ-CR and MCQ-C_{30} that enable better coverage of POS and NEG in younger children. The use of orally posed open questions reveals another approach for assessing POS and NEG in even younger children, thus enabling us to investigate the onset of such beliefs about worry[70].

What evidence is there for positive relationships between POS, NEG, and meta-worry with each other, worry, and anxiety in children and adolescents?

NEG correlated in all 14 studies[24,25,26,28,30,51,64-69,75,82] with worry and proved to be an independent predictor of worry in three[23,65,73] out of three studies. Meta-analysis showed large overall correlation between NEG and worry.

NEG also correlated with anxiety in 17[24-26,30,52-55,64,66-68,76-79,82] of 19 studies. Benedetto *et al*[49] study 2 revealed a correlation in their clinical sample only. Surprisingly, another study showed a significant negative relationship of medium effect size between NEG measured with MCQ-30 and anxiety in high school students [55]. The questionnaires used had not been adapted or evaluated for use in adolescents; their contradictory result may be attributable to their not mentioning any specific age range[55]. Overall, the correlation between NEG and anxiety in our meta-analysis revealed was large. NEG predicted anxiety uniquely in three[23,68,75] out of four studies. One study found that NEG was not a significant predictor of anxiety, however[25]. Eight[23,24,49,52,53,74,79,80] out of 10 studies that compared clinical and non-clinical samples showed higher NEG in participants with anxiety disorders, a finding that also supports the metacognitive model. Two studies[27,28] detected no significant group differences.

For POS, 12[24,28,51,64-69,71,72,82] out of 16 studies showed a significant positive relationship with worry, while correlations failed to reach significance in four studies [26,30,48,74]. Meta-analysis resulted in a small overall effect size for the correlation between POS and worry. POS predicted worry in three[23,71,73] out of four studies, while it was not significant in one study[65].

POS correlated with anxiety in 12[24,30,52-54,64,66-68,76-78] out of 19 studies. Studies 1 and 2 of Benedetto *et al*[49] did identify significant correlations but only in their clinical subgroup, while Reinholdt-Dunne *et al*[79] detected a significant correlation in their non-clinical subgroup. In fact, four studies[25,26,55,82] failed to indicate any significant correlations between POS and anxiety. Meta-analysis demonstrated a small to medium effect size for the correlation between POS and anxiety. POS proved to be unique predictors of anxiety in one[68] of three studies, while two studies[73,80] failed to prove POS as a significant predictor. Clinical groups scored higher on POS than non-clinical groups in four[23,24,52,79] out of 10 studies, while six[27,28,49,53,74,80] studies revealed no significant group differences.

Table 5 Measurements of metacognitive beliefs about worry and meta-worry

Measure	Items	Scales	Answer format	Values for reliability	Age	*k*
MCQ-C	24	4	Do not agree (1) to agree very much (4)	POS: α = 0.46 - 0.89, *rtt* = 0.82; NEG: α = 0.60 - 0.95, *rtt* = 0.76[25-28,49,51,52,57,64,65,72,73,74,78]	7-17	22
MCQ-A	30	5	Do not agree (1) to agree very much (4)	POS: α = 0.80 - 0.90, *rtt* = 0.66; NEG: α = 0.80 - 0.87, *rtt* = 0.71[24,53,54,81,82]	11-17	9
MCQ-C_{30}	30	5	Not at all (1) to completely (4)	POS: α = 0.64 - 0.73; NEG: α = 0.71 - 0.79[23,76,93]	7-17	8
MCQ-30	30	5	Do not agree (1) to agree very much (4)	POS: α = 0.88; NEG: α = 0.77[67]	15-18	3
MCQ-CR	30	5	Not true (1) to Very true (4); I do not understand	POS: α = 0.77; NEG: α = 0.80[30]	7-12	1
MKF-K	30	4	Not at all (1) to completely (4)	POS: α = 0.73; NEG: α = 0.70[68]	7-14	1
MWQ	7	2	Never (1) to almost always (4)	α = 0.80 - 0.82[73]	11-18	1
WW-II	25	5	Not at all (0) to incapacitating (4)	α = 0.90[71]	7-18	1
Interview	2	2	Open questions	κ = 0.61[70]	6-10	1

α: Cronbach's Alpha; *rtt:* Test-retest-reliability; κ: Cohen's kappa; *k*: Number of included studies which used the measure; MCQ-30: Metacognitions Questionnaire - 30-Item Version; MCQ-A: Metacognitions Questionnaire - Adolescent Version; MCQ-C: Metacognitions Questionnaire for Children; MCQ-CR: Revised Metacognitions Questionnaire for Children; MCQ-C30: Metacognitions Questionnaire for Children - 30 Item version; MKF-K: Metacognition questionnaire for children; MWQ: Meta-Worry Questionnaire; WW-II: Why Worry-II; POS: Positive beliefs about worry; NEG: Negative beliefs about worry.

Correlations between POS and NEG were reported as significant in 12[30,51,52,55,64-69,76,77,81] out of 19 studies, whereas that finding applied to only one of two subgroups in Studies 1 and 2 of Benedetto *et al*[49] and a study by Reinholdt-Dunne *et al*[79]. Meta-analysis demonstrated a small to medium effect size.

These mixed results partly support the metacognitive model as well, but NEG seem to have a generally more stable effect on worry and anxiety than POS. POS correlations were quite smaller (small to medium effect sizes) while NEG correlations were large. This is not surprising since NEG revealed medium to large correlations with anxiety and worry in adults, while POS result in small to medium correlations with anxiety and worry[83,85,86]. Meta-analysis revealed a smaller effect for the correlation between POS and NEG (small to medium), while correlations for NEG with anxiety and worry are large - evidence that concurs with studies from adult research[83,85,86]. To evaluate conclusively the causal claims of the metacognitive model for children, longitudinal studies are needed. However, most of the studies we included applied a cross-sectional design that precludes such conclusions. Only 10 studies compared clinical to non-clinical samples. Future studies should compare POS, NEG, and meta-worry in clinical and non-clinical samples to validate further the metacognitive model of GAD in childhood and youth. For more information about the specific influence of NEG and meta-worry in the development of GAD, patients presenting different anxiety disorders should be compared also, since the results here are far from clear. In total, the overall situation that this systematic review and meta-analysis portrays indicates that NEG play an especially relevant role in worry and anxiety in children and adolescents, and that there is ample evidence from studies that supports the applicability of the metacognitive model of GAD in childhood and youth.

At what age do children report POS, NEG, and meta-worry, and does age play a role in the relationships with worry and anxiety?

Fourteen studies in total included samples of children aged 7 years and upwards. None of those studies investigated the age of onset of metacognition about worry explicitly. To explore how well children understand questionnaire items, White and Hudson[30] added a response option for not-understanding in the MCQ-CR, and their results support an improvement in how well items are understood from the age 7 to 12 years. Nevertheless, at least 75% of 7- to eight-year-olds understood every MCQ-CR

item. Only one study investigated even younger children[70]. The authors posed open-ended questions verbally to assess POS and NEG in 6-year-olds and concluded that these children are capable of understanding and can describe beliefs about worry, as more than half of the 6- to 10-year-olds stated POS, and almost 8 out of 10 children stated NEG. Response frequencies did not differ with age. Although children are less capable of introspection at 5 years of age than 7- or 8-year-olds[33,35], this result implicates that the metacognitive abilities needed to perceive and describe when worry arises and what feelings and thoughts are associated with it are already developed by the age of 6 years. It thus seems possible that we are underestimating the metacognitive ability of young children[36]. This could also be because POS and NEG are usually surveyed using questionnaires.

Most of the included studies revealed no significant associations between the participants' age and NEG[24,27,30,54,76,79,82] or POS[24,27,30,72,76,77,79,81,82]. Two studies even demonstrated negative correlations between age and NEG[77,81]. We cannot therefore assume any increase in POS and NEG with rising age. However, one study[54] did show a positive correlation between POS and age. We analyzed mean age as a covariate in meta-regressions as a potential source of variance, but the results were not significant, thus we cannot assume that mean age is a relevant source of variance. Because of the rather small number of included studies in meta-regressions (range: k = 11-16) and the substantial heterogeneity as demonstrated by Q- and I^2-statistics, there might be insufficient power to demonstrate mean age's moderating effect[87]. Our results therefore do not allow us to assume that mean age has a zero-effect on correlations between POS and NEG with each other, worry, and anxiety. Nevertheless, our overall results suggest that POS and NEG do not vary much with age and that the metacognitive model of GAD can be applied to a broad age range of seven to 18 years.

Which methods are currently applicable to assess POS, NEG, and meta-worry in childhood and youth?

The studies included in this review indicate that MCQ-family of questionnaires are the ones most widely used in research and clinical practice to measure metacognitive beliefs in childhood and youth. We identified six derivates of the MCQ in this review. The MCQ-C, applied in 22 studies, was most frequently administered in children and adolescents aged 7 to 18 years. For youth between 11 and 17 years, the MCQ - Adolescent Version was used in nine studies. MCQ-C_{30} was also used in 7- to 17-year-olds in eight studies. Since each study we included originated from a single research group, we may have overestimated the frequency of use. The MCQ-30, designed for adults, was administered by three study groups in adolescents between 15 and 18 years of age without any adaptations for that age group. Other MCQ-derivates were only used in one study each. The MCQ-CR was especially designed to be better understandable for 7- and 8-year-olds[30] but was not distributed further. One study used the German questionnaire Metakognitionsfragebogen für Kinder[68]. To measure exclusively POS, Why Worry-II was used without pretesting or adaptation in a sample of 7- to 18 year-olds[71].

One study posed open-questions to assess verbally POS and NEG in children from the age of 6 to 10 years but detected no age-related differences in POS or NEG[70]. Such interview approaches represent an alternative method when surveying young children who may not yet be able to read well enough. To define the onset of POS and NEG more specifically, future research should also attempt to replicate the results of Wilson and Hughes[70] with a larger sample and perhaps include even younger children. An interview-format was also applied in the dissertation of Bacow[88], the MCQ-C author who designed the "Evaluations of Worries and Thoughts Interview for Children" (EWTI-C) to survey worry and associated beliefs. While the MCQ-C's results were covered in the paper of Bacow *et al*[28], no EWTI-C data have been published yet. Interestingly, when measured with the EWTI-C, POS and NEG did not correlate with worry at all, and participants with anxiety disorder reported more NEG, but not POS, than non-clinical controls[88]. This indicates a need for valid and reliable methods to measure metacognition in childhood and youth. More recently, thanks to the availability of the MCQ-CR and MCQ-C_{30}, two promising adaptations of the MCQ have been added and should be further investigated. Although meta-worry plays an important role in the metacognitive model, only one study investigated this construct using the meta-worry questionnaire with children aged 11 years[73]. This questionnaire has not yet been validated or adapted for children and adolescents. We need to improve and modify suitable instruments for measuring meta-worry, and it deserves more attention in future research.

Limitations

Some limitations need to be considered: First, the results we extracted are mainly cross-sectional and thus preclude any causal conclusions. Longitudinal studies are needed to support the metacognitive model's causal assumptions despite the overall relationship trends the cross-sectional data from this review has revealed so far.

Second, the broad heterogeneity revealed across the various meta-analyses we conducted should be considered a limitation. The amount of genuine variance not attributable to chance was medium to large, as the heterogeneity values indicate (I^2 = 67% and 95%). Mean age was assessed as a covariate by meta-regression to see whether age plays a role in relationships between POS and NEG with worry and anxiety, but it did not explain variance. Other sources of variance might include differences in assessment methods for POS, NEG, anxiety and worry, sample types (clinical *vs* non-clinical), percentage of comorbid disorders in clinical samples, and gender distribution. Additional meta-regressions for these potential covariates could help to explain the amount of variance among the included studies.

Third, some studies covered a broad age range[28,51,69,78,79], limiting specific interpretations of potential developmental patterns specific to different age groups. We chose mean age as a covariate for meta-regression, but the ages of all participants might not have been accurately represented. Our results can thus only reflect the mean age of the samples and must be interpreted with caution for aggregation bias[89].

Fourth, only studies with clinical samples were included if they exclusively assessed patients with DSM-5[40] listed anxiety disorders, but three studies[27,28,52] contained clinical subgroups with post-traumatic stress disorder or OCD, as they had been included in anxiety disorders in the DSM's earlier fourth edition[90]. Moreover, 60% of non-clinical participants in one study presented subclinical anxiety symptoms[28].

Fifth, to measure POS and NEG, some Cronbach's alpha values for the MCQ-C[25,27,28,52,57,64,65,72,73] and MCQ-C_{30}[60,76] fell below the recommended level of 0.70 for exploratory research as recommended by Nunnaly and Bernstein[91]. Moreover, the MCQ-C does not seem to be ideally suitable for use in younger children, as 35.8% to 78.6% of children aged 7 to 8 years did not fully understand six items[52]. As the MCQ-C was used in k = 22 studies and the MCQ-C_{30} in k = 8 studies, this factor should be considered a limitation.

Sixth, we could include only one unpublished study as gray literature[68], therefore the risk of publication bias should be considered a limiting factor.

CONCLUSION

In conclusion, the studies included in this review demonstrate that POS and NEG are measurable by administering questionnaires in children from 7 years of age upwards, and even children aged as young as 6 years can already name them verbally. Furthermore, POS and NEG do not seem to vary with age in childhood and youth. NEG shows strong overall correlations with worry and anxiety over different age groups, highlighting their relevance in the development and maintenance of anxiety disorders and confirming the metacognitive model's implications. POS' smaller effect sizes and inconsistent findings suggest that these play a subordinate role, in line with the evidence from adult studies[83,85,86]. The current research data reveal quite large heterogeneity between studies that cannot be attributed to the influence of mean age. Nor can any conclusions about the influence of meta-worry on anxiety disorders be drawn. Measurements of meta-worry in children and adolescents are thus needed, and measurements of POS and NEG for young children require further research. Longitudinal studies could enable clearer conclusions to be made on causal relationships between the metacognitive model's relevant constructs.

ARTICLE HIGHLIGHTS

Research background

The metacognitive model of generalized anxiety disorder has been applied to children and youth in different studies. Results mostly support its validity, but the roles of positive metacognitive beliefs about worry (POS), meta-worry, and age-effects do not appear to be fully clarified yet.

Research motivation

Summarizing the current research on relationships, age-effects, and measurements for POS, negative metacognitive beliefs about worry (NEG) and meta-worry in childhood and youth are both timely and worthwhile.

Research objectives

Relationships between POS, NEG, and meta-worry with each other, worry, and anxiety, and possible age-effects for these relationships were analyzed. Assessment methods POS, NEG and meta-worry for children and adolescents were examined.

Research methods

A literature search was carried out in the electronic databases PsycINFO, PubMed, PSYNDEX, and ERIC in 2017 and updated in 2020. Empirical research in German or English language on metacognition was included with child and adolescent samples diagnosed with anxiety disorders or healthy controls if POS, NEG, or meta-worry was measured. Meta-analysis for reported correlations between these metacognitions and anxiety or worry was carried out with RevMan 5.4.1, assuming random-effects models. Meta-regressions with mean age as the covariate were performed *via* the online tool MetaMar 2.7.0.

Research results

Overall, we included k = 48 studies in this systematic literature review and of those, k = 24 studies fulfilled our inclusion criteria for meta-analysis. Systematic review and meta-analysis showed that POS and NEG correlate with worry and anxiety. Mean age was not a significant covariate in meta-regressions. Only one study measured meta-worry. We identified eight questionnaires and one interview approach for assessment of metacognitive beliefs.

Research conclusions

Our overall results support the applicability of the metacognitive model of generalized anxiety disorder in childhood and youth. NEG play an especially relevant role in worry and anxiety in children and adolescents, while conclusions about meta-worry's influence cannot be drawn. Most included studies used a cross-sectional design and thus preclude causal conclusions. Metacognitive beliefs do not seem to vary with age and appear to be measurable in children from 7 years upwards.

Research perspectives

Longitudinal studies and research on the impact and measurement of meta-worry would be beneficial. Measurements applying to young children should undergo further investigation.

ACKNOWLEDGEMENTS

The authors wish to thank Hannah Grote for help with risk of bias rating and all members of the working unit Clinical Child and Adolescent Psychology (Department of Psychology, University of Marburg) for their support throughout this study.

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World J Psychiatr 2021 September 19; 11(9): 659-680

DOI: 10.5498/wjp.v11.i9.659

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Deep brain stimulation for obsessive-compulsive disorder: A systematic review of worldwide experience after 20 years

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Supported by Carlos III Health Institute, No. PI16/00950 and No. PI18/00856; and FEDER funds ('A way to build Europe').

Conflict-of-interest statement: All the authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in

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Abstract

BACKGROUND

Twenty years after its first use in a patient with obsessive-compulsive disorder (OCD), the results confirm that deep brain stimulation (DBS) is a promising therapy for patients with severe and resistant forms of the disorder. Nevertheless, many unknowns remain, including the optimal anatomical targets, the best stimulation parameters, the long-term (LT) effects of the therapy, and the clinical or biological factors associated with response. This systematic review of the articles published to date on DBS for OCD assesses the short and LT efficacy of the therapy and seeks to identify predictors of response.

AIM

To summarize the existing knowledge on the efficacy and tolerability of DBS in treatment-resistant OCD.

METHODS

A comprehensive search was conducted in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020, using the following strategy: "(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS)." Clinical trials and observational studies published in English and evaluating the effectiveness of DBS for OCD in humans were included and screened for relevant information using a standardized collection

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 28, 2021
Peer-review started: February 28, 2021
First decision: April 20, 2021
Revised: May 2, 2021
Accepted: August 18, 2021
Article in press: August 18, 2021
Published online: September 19, 2021

P-Reviewer: Li Y, Zhang C
S-Editor: Gao CC
L-Editor: A
P-Editor: Ma YJ

tool. The inclusion criteria were as follows: a main diagnosis of OCD, DBS conducted for therapeutic purposes and variation in symptoms of OCD measured by the Yale-Brown Obsessive-Compulsive scale (Y-BOCS) as primary outcome. Data were analyzed with descriptive statistics.

RESULTS

Forty articles identified by the search strategy met the eligibility criteria. Applying a follow-up threshold of 36 mo, 29 studies (with 230 patients) provided information on short-term (ST) response to DBS in, while 11 (with 155 patients) reported results on LT response. Mean follow-up period was 18.5 ± 8.0 mo for the ST studies and 63.7 ± 20.7 mo for the LT studies. Overall, the percentage of reduction in Y-BOCS scores was similar in ST (47.4%) and LT responses (47.2%) to DBS, but more patients in the LT reports met the criteria for response (defined as a reduction in Y-BOCS scores > 35%: ST, 60.6% *vs* LT, 70.7%). According to the results, the response in the first year predicts the extent to which an OCD patient will benefit from DBS, since the maximum symptom reduction was achieved in most responders in the first 12-14 mo after implantation. Reports indicate a consistent tendency for this early improvement to be maintained to the mid-term for most patients; but it is still controversial whether this improvement persists, increases or decreases in the long term. Three different patterns of LT response emerged from the analysis: 49.5% of patients had good and sustained response to DBS, 26.6% were non responders, and 22.5% were partial responders, who might improve at some point but experience relapses during follow-up. A significant improvement in depressive symptoms and global functionality was observed in most studies, usually (although not always) in parallel with an improvement in obsessive symptoms. Most adverse effects of DBS were mild and transient and improved after adjusting stimulation parameters; however, some severe adverse events including intracranial hemorrhages and infections were also described. Hypomania was the most frequently reported psychiatric side effect. The relationship between DBS and suicide risk is still controversial and requires further study. Finally, to date, no clear clinical or biological predictors of response can be established, probably because of the differences between studies in terms of the neuroanatomical targets and stimulation protocols assessed.

CONCLUSION

The present review confirms that DBS is a promising therapy for patients with severe resistant OCD, providing both ST and LT evidence of efficacy.

Key Words: Deep brain stimulation; Obsessive-compulsive disorder; Predictors of response; Side effects; Short-term; Long-term

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Core Tip: This systematic review describes worldwide experience in the use of deep brain stimulation (DBS) in severe resistant patients with obsessive-compulsive disorder over the last twenty years, comparing short-term (ST) and long-term (LT) response to the treatment (in 230 and 155 patients respectively). Both ST and LT studies report similar, stable reductions in severity of around 47%, although the number of patients who met the criteria for response was significantly higher in the LT studies (60.6% *vs* 70.7%). DBS is a safe and well-tolerated technique, since most side effects are mild and reversible on adjusting stimulation parameters. However, no clear predictors of response can be established at present.

Citation: Mar-Barrutia L, Real E, Segalás C, Bertolín S, Menchón JM, Alonso P. Deep brain stimulation for obsessive-compulsive disorder: A systematic review of worldwide experience after 20 years. *World J Psychiatr* 2021; 11(9): 659-680
URL: https://www.wjgnet.com/2220-3206/full/v11/i9/659.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i9.659

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by the presence of persistent intrusive thoughts, images or urges (obsessions) that lead to compulsions, repetitive mental or motor acts, or avoidance behaviors, in order to reduce anxiety[1]. OCD has a lifetime prevalence of 2%-3%. It begins in childhood, puberty or early adult life, and thus affects a critical period in relational and academic development[2,3]. The standard treatment for OCD combines psychotropic medication - typically serotonin reuptake inhibitors and antipsychotic potentiation - and cognitive behavioral therapy (CBT), mainly exposure with response prevention. However, around 10% of patients continue to present chronic and severe obsessive-compulsive symptoms despite exhausting all available pharmacological strategies and undergoing intensive behavior therapy[4,5]. In this group of severely disabled OCD patients, for some decades now neurosurgical interventions have been considered as a potential treatment, in spite of the possible risks.

Beyond ablative surgery, advances in many areas of neurosurgery and neuroimaging over the last 20 years have made it possible to test the capacity of different brain stimulation techniques. These techniques include deep brain stimulation (DBS) for modulating the activity of dysfunctional brain areas located in, or intimately connected with, the cortico-striato-thalamo-cortical circuitry in treatment-refractory OCD[6]. DBS was first used in 1999 as a surgical option for patients with severe OCD who had not responded to other treatments[7], but it was not until 2009 that the US Food and Drug Administration and Conformité Européenne approved it under the Humanitarian Device Exemption Program[8]. This new status means that DBS may be used as an alternative to more invasive procedures, such as anterior capsulotomy, for the treatment of chronic, severe, treatment-resistant OCD. Indeed, DBS is a reversible, focal, and adjustable neuromodulation technique that is usually well tolerated. Serious adverse effects are infrequent; they are typically psychiatric (*e.g.*, hypomania, sleep complaints, disinhibition, and depression)[9,10], and can be minimized by adjusting the stimulation parameters[11]. Although adverse effects have been described in somatic domains (*e.g.*, weight change, sexual complaints, infection, and gastrointestinal symptoms) and neurological domains (*e.g.*, headache, paresthesia, sensorial complaints, or cognitive difficulties), they are relative-ly rare[12,13].

Literature reports indicate that, to date, more than 300 patients with OCD have undergone surgery for DBS implantation. Among these reports, three meta-analyses[9-11] have reported that approximately 60% achieved reductions of > 35% on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS, the gold standard of OCD symptom assessment), a rate accepted as indicating response to treatment[14,15]. This mean reduction in the Y-BOCS score is reported to range from 38.6% to 45.1%, and the major differences between studies has been attributed to the heterogeneity of the targets stimulated and the parameters programmed[16,17]. Recently, studies have begun to publish data on the long-term (LT) outcome of these patients[18-22]. Despite all these advances, however, and 20 years after the first DBS implantation in a patient with OCD, our knowledge of the benefits and risks of DBS use in OCD is still limited, due to the small sample sizes, the lack of adequate control conditions, and the heterogeneity of the anatomical targets and stimulation parameters applied. Therefore, a systematic and critical review of all the data published to date can help us resolve some of the doubts regarding the extension and likelihood of treatment response to DBS, the need for concomitant pharmacological or behavioral treatments after implantation, the recommended duration of stimulation in both responsive and non-responsive patients, and the risk of severe adverse effects.

Therefore, the aim of this systematic review is to summarize the existing knowledge on the efficacy and tolerability of DBS in treatment-resistant OCD and to compare the short-term (ST) and LT results. This analysis should indicate whether differential response patterns exist and whether response predictors can be established so as to optimize the use of DBS in patients with OCD.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance[23,24]. Studies with ST and LT follow-up periods are referred to as “ST studies” and “LT studies” respectively.

Search strategy

A comprehensive search was conducted in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020, using the following strategy: "(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS)." The search identified a limited number of studies and was therefore completed by manual selection of relevant studies included in the reference lists of previously published articles. Any available meta-analyses and systematic reviews were also assessed in order to include all references.

Eligibility criteria

We conducted a systematic review of studies evaluating the effectiveness of DBS for OCD in humans, searching for both clinical trials and observational studies. The inclusion criteria were as follows: (1) A main diagnosis of severe and disabling OCD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth or fifth edition[1,25], regardless of comorbidities; (2) DBS conducted for therapeutic purposes; (3) A primary outcome of variation in OCD symptoms measured by the Y-BOCS[14,15]. The Y-BOCS is the gold standard for OCD symptom assessment and was used in all studies assessing response to DBS in OCD; (4) Publication in English; and (5) Randomized clinical trials (parallel or crossover) or observational studies designs. Articles were excluded if their focus was sham stimulation, neuroanatomy, functional imaging, or neurophysiology.

Study selection and outcome measures

Articles were initially extracted and screened (title, abstract, and full article) by one reviewer (Mar-Barrutia L) with regard to the eligibility criteria and were subsequently reviewed by a second reviewer (Alonso P) to confirm their eligibility. Disagreements were resolved by consensus. The following data were then extracted: authors, year of publication, sample size, and study design; patient age, sex, and illness duration; DBS target site and follow-up since implantation; Y-BOCS, depression assessment, and global function (*e.g.*, Global Assessment of Functioning, GAF score) at baseline and last follow-up; adverse effects; and suicide attempts and/or death by suicide. Data were double-checked to exclude duplication. If a patient was included in more than one study, only their most recent/most detailed data were considered.

Risk of bias assessment

We used the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias in randomized controlled trials (RCT)[26], classifying the risk as low, high, or unclear risk in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. To assess the risk of bias in observational studies we used the Newcastle-Ottawa Scale[27] (Table 1 and Table 2).

Ethics

The review did not require ethics committee approval because it analyses anonymous, previously published information.

RESULTS

Study characteristics: ST vs LT follow-up

Using the search strategy, we identified 896 articles for abstract review. Of these, 40 met the eligibility criteria (Figure 1), and a further three meta-analyses were also assessed[9-11]. Based on a follow-up threshold of 36 mo, we classified 29 articles as ST (230 cases) and eleven as LT (155 cases). Some LT studies described the LT follow-up of patients who had previously been included in ST studies (a total of 41 cases).

To assess the differences between ST and LT studies, the mean values for clinical and methodological variables were compared between the two study types (Table 3). Most ST studies (23) and most LT studies (9) were observational. The mean follow-up period in the ST studies was 1.5 years and in the LT studies 5.3 years, and the mean sample sizes were 7.9 and 14 respectively. No significant differences were detected in gender distribution, mean age at inclusion, mean Y-BOCS scores at baseline and last observation, or the percentage of reduction in Y-BOCS scores. However, the mean percentage of responders (patients with a > 35% reduction in Y-BOCS scores) rose from 60.6% in the ST studies to 70.7% in the LT studies. There was considerable

Table 1 Risk of bias for randomized controlled trials

Ref.	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Abelson *et al* [67], 2005			-	-	+		
Barcia *et al* [32], 2019		+	-	-	-		
Goodman *et al* [16], 2010			-	-	+		
Huff *et al*[31], 2010					+		
Luyten *et al* [20], 2016	+		-	-			
Tyagi *et al* [17], 2019		+			+	+	
Welter *et al* [39], 2020		+	-	-	-		

+: High risk of bias; -: Low risk of bias. If there is no sign, the risk of bias is uncertain.

variability in the programming parameters reported in the studies: both monopolar and bipolar stimulation were used, and the average frequency of stimulation ranged from 100-130 Hz, average pulse width from 60-450 μs, and average voltage from 2-7.4 V.

The level of depression, as assessed by different scales, was reported more frequently in LT than in ST studies. However, depressive symptoms improved regardless of the follow-up duration. The characteristics and results for the ST and LT studies, grouped into RCT and non-RCT designs, are presented in Tables 4-7.

Primary outcomes: Obsessive symptoms

The minimum Y-BOCS score required for DBS implantation was 30-32 in most studies, a score range consistent with severe illness; some studies applied less restrictive inclusion criteria (scores > 24)[28-32]. The mean changes in Y-BOCS scores from pre- to post-treatment were similar in the ST studies (change from 33.0 to 17.2) and the LT studies (change from 34.4 to 18.0). Thus, the percentage reduction in Y-BOCS scores remained stable when comparing ST and LT responses to DBS (47.4% *vs* 47.2%), but significantly more patients in the LT reports met the criteria for response (ST: 60.6%, *vs* LT: 70.7%). These results are consistent with those of previous meta-analyses[9-11].

Given that DBS has only been authorized for the treatment of OCD for 20 years, the evidence available on the LT clinical course remains limited. Our systematic review includes information on 155 patients from different parts of the world treated for a mean follow-up period of 5.3 years. Those responding to DBS, either completely or partially, tended to achieve the maximum symptom reduction in the first 12-14 mo after implantation[19,21]. Graat *et al*[19] followed the largest sample to date (50 patients) from 3 years to 13 years and found that most responders at LT follow-up had responded in the first year. This initial period of improvement coincided with a time when more stimulator adjustments were performed and the patient engaged in simultaneous behavioral therapy. Holland *et al*[21] reported that their nine patients needed > 1 year to achieve maximum improvement, but their mean results of 32.5 mo were seriously affected by an outlier with a significantly prolonged response time. After excluding this subject, the mean response time fell to 14.6 mo, again suggesting that response in the first year significantly predicts the extent to which an OCD patient will benefit from DBS.

Reports indicate a consistent tendency for the improvement to be maintained to the mid-term for most patients[19,22,33-38], but it is controversial whether this improvement persists, increases or decreases in the LT. Winter *et al*[28], Holland *et al*[21] and Mallet *et al*[22] found progressive decreases in obsessive symptoms over time. For example, while Mallet *et al*[22] reported that the mean Y-BOCS score decreased by one point per year up to 46 mo, Graat *et al*[19] reported a slight increase of 1.8 points at the end of their follow-up period. Luyten *et al*[20] also reported a 66% reduction in Y-

Table 2 Risk of bias for non-randomized controlled trials

Ref.	Selection	Comparability	Outcome
Anderson and Ahmed[74], 2003	++	+	++
Aouizerate *et al*[75], 2009	++	+	+++
Azriel *et al*[76], 2020	++	+	+++
Chabardes *et al*[29], 2020	++	+	++
Chang *et al*[77], 2017	++	+	+++
Choudhury *et al*[78], 2017	++	+	+++
Coenen *et al*[79], 2017	++	+	+++
Denys *et al*[44], 2020	++	+	++
Doshi *et al*[80], 2019	++	+	+++
Farrand *et al*[42], 2018	++	+	+++
Fayad *et al*[33], 2016	++	+	+++
Franzini *et al*[81], 2010	+++	+	+++
Gabriëls *et al*[53], 2003	++	+	+++
Graat *et al*[19], 2020	++	+	+++
Grant *et al*[34], 2016	++	+	+++
Greenberg *et al*[36], 2010	++	+	+++
Gupta *et al*[35], 2019	++	+	+++
Holland *et al*[21], 2020	++	+	+
Huys *et al*[30], 2019	++	+	+++
Islam *et al*[40], 2015	++	+	+++
Jiménez *et al*[55], 2013	++	+	+++
Lee *et al*[37], 2019	++	+	+++
Maarouf *et al*[45], 2016	+++	+	++
Mallet *et al*[22], 2019	++	+	+++
Menchón *et al*[13], 2021	++	+	++
Mulders *et al*[82], 2017	++	+	+++
Plewnia *et al*[83], 2008	++	+	+++
Polosan *et al*[38], 2019	++	+	+++
Roh *et al*[61], 2012	++	+	+++
Sachdev *et al*[84], 2012	++	+	++
Senova *et al*[85], 2020	++	+	+++
Tsai *et al*[49], 2012	++	+	++
Winter *et al*[28], 2021	++	+	+++

Each "+" symbol indicates lower risk of bias.

BOCS scores 4 years after DBS implantation, which had become a 45% reduction by 14 years. The percentage of responders (67%) remained significant at the end of follow-up.

The lack of individual data from the studies analyzed rules out a statistical classification of the LT evolution of OCD after treatment with DBS. Nevertheless, the data available suggest at least three patterns of LT response. First, 26.6% of subjects in all the studies were non responders, in whom the clinical effect was negligible despite all attempts to adjust the stimulation parameters for months or years[21,28,29,33,39,40]. Second, 49.5% of patients were responders who showed a maximum improvement in

Table 3 Differences in mean characteristics between the short-term and long-term studies

Characteristic	Short-term		Long-term	
	mean ± SD	Range	mean ± SD	Range
Sample size, *n*	7.9 ± 13.6	1-70	14 ± 14.4	1-50
Female, %	54 ± 36.9	0-100	61.5 ± 22	33-100
Average age, yr	41.7 ± 9.9	28-72	40.5 ± 4.3	32-45
Average duration of illness, yr	24 ± 16.4	5-52	20.4 ± 3.2	16-25
Follow-up since DBS, mo	18.5 ± 8	7-36	63.7 ± 20.7	38-96
Follow-up since DBS, yr	1.5 ± 0.6	1-2.7	5.3 ± 1.7	3-7.7
Baseline Y-BOCS, mean score	33 ± 3.7	19-39	34.4 ± 1.7	32-38
Last Y-BOCS, mean score	17.2 ± 7.4	1-31	18 ± 3.2	11-21
Y-BOCS improvement, %	47.4 ± 21	10-97	47.2 ± 9.9	36-71
Responders, %	60.6 ± 36.2	0-100	70.7 ± 24.8	22-100
	Yes/no		**Yes/no**	
RCT	6/23		1/10	
Depression assessment	21/6		9/11	
Depression improvement	15/4		8/1	
Functionality assessment	16/13		7/4	
Functionality improvement	14/1		7/0	

DBS: Deep brain stimulation; NR: Not reported; RCT: Randomized controlled trial; Y-BOCS: Yale-Brown Obsessive Compulsive scale.

the first 12-24 mo and remained in stable remission for years. A third group of partial responders (22.5% of patients) improved at some point during treatment, but then experienced relapses during follow-up. Although some of the relapses among partial responders were linked to external stressors, such as the loss of a family member[19], device-related events (*e.g.*, battery depletion[41]), or comorbid conditions (*e.g.*, depression or generalized anxiety[42]), no clear external stressors have been associated with relapses in other patients with fluctuating courses[33]. Thus, some patients will be expected to show an oscillating response to DBS that we still cannot explain. Virtually all studies agree that battery depletion is accompanied by severe symptom deterioration, which may be very abrupt[22]. While this finding reinforces the therapeutic benefit of DBS for OCD, it also highlights the need to monitor patients closely for this risk.

Secondary outcomes: Depression and global function

Depressive symptoms: Depressive disorders are the most frequent comorbidity among patients with OCD treated by DBS[10,41,43], with 63.3% being diagnosed with any mood disorder and 40.7% meeting the diagnostic criteria for a major depressive disorder[2]. Twenty-nine of the 40 studies assessed changes in depressive symptoms after DBS implantation, but the use of seven different scales (HDRS, MADRS, BDI, DASS, QIDS, IDS-30, POMS) makes direct comparisons difficult. In most studies, maximum improvement of depressive symptoms was observed in the first year after DBS therapy, regardless of the follow-up period. These improvements tended to parallel those for obsessive symptoms and tended to endure over time[20,21,36] (Table 2), but there was not always a clear correlation. Winter *et al*[28], for example, found a greater decrease in the MADRS score in patients who responded to DBS, whereas both Denys *et al*[44] and Graat *et al*[19] described a significant improvement in depressive symptoms in patients who experienced no change in their OCD symptomatology. In fact, these patients requested continued stimulation despite an improvement in obsessive symptoms. The same research group has previously described the improvement process as a sequence that begins with the amelioration of affective symptoms (in seconds), followed by anxious symptoms (in minutes), obsessive symptoms (in days), and compulsions (in weeks or months)[43]. Unfortunately, a significant worsening of mood symptoms in some patients who respond to

Table 4 Participant characteristics in the short-term studies

	Ref.	*n*	Female %	Average age (yr)	Average duration of illness (yr)	Average follow-up since DBS implantation (mo)	Target site
RCT	Abelson *et al*[67], 2005	4	50	40.2	22.5	12.8	ALIC
	Barcia *et al*[32], 2019	7	57.1	35.2	25.3	21	NAcc/CN
	Goodman *et al*[16], 2010	6	66	36.2	24	12	VC/VS
	Huff *et al*[31], 2010	10	40	36.3	22.2	12	NAcc
	Tyagi *et al*[17], 2019	6	16.6	45.5	24.1	12	VC/VS, STN, VC/VS/STN
	Welter *et al*[39], 2020	8	12.5	42.5	NR	22	STN, CN, NAcc
Non-RCT	Anderson and Ahmed[74], 2003	1	100	35	10	10	ALIC
	Aouizerate *et al*[75], 2009	2	0	51	33.5	15	NAcc/CN
	Azriel *et al*[76], 2020	1	100	67	44	16	amGPI
	Chabardes *et al*[29], 2020	19	63.1	39	20.7	24	STN
	Chang *et al*[77], 2017	1	100	28	8	12	VC/VS
	Coenen *et al*[79], 2017	2	0	41.5	29	12	MFB
	Denys *et al*[44], 2020	70	69	41.7	25	12	ALIC
	Doshi *et al*[80], 2019	1	100	42	NR	12	NAcc
	Farrand *et al*[42], 2018	7	57.1	46	25	31	NAcc or BNST
	Franzini *et al*[81], 2010	2	0	37	21.5	25.5	NAcc
	Gabriëls *et al*[53], 2003	3	67	41.7	24.3	27	NAcc/ALIC
	Grant *et al*[34], 2016	1	0	30	5	36	NAcc
	Huys *et al*[30], 2019	20	50	40.1	26.1	12	ALIC-NAcc
	Islam *et al*[40], 2015	8	17	45.8	30.2	25	BNST, NAcc
	Jiménez *et al*[55], 2013	6	50	34.7	16.2	24	ITP
	Maarouf *et al*[45], 2016	4	75	39.3	23.5	11.5	MD/VA
	Menchón *et al*[13], 2021	29	52	41	24.5	12	ALIC
	Mulders *et al*[82], 2017	1	100	49	34	24	VC/VS
	Plewnia *et al*[83], 2008	1	100	51	NR	24	ALIC/NAcc
	Roh *et al*[61], 2012	4	25	45.5	24.2	24	VC/VS
	Sachdev *et al*[84], 2012	1	100	32	28	7	NAcc
	Senova *et al*[85], 2020	1	100	72	52	36	STN
	Tsai *et al*[49], 2012	4	0	25.5	8.3	15	VC/VS

ALIC: Anterior limb on internal capsule; amGPI: Anteromedial globus pallidus internus; BNST: Bed nucleus of stria terminalis; CN: Caudate nucleus; ITP: Inferior thalamic peduncle; MD/VA: Medial dorsal and the ventral anterior nucleus of the thalamus; MFB: Medial forebrain bundle; NAcc: Nucleus

accumbens; NR: Not reported; RCT: Randomized controlled trial; VC/VS: Ventral caudate/ventral striatum.

Table 5 Participant characteristics in the long-term studies

	Ref.	*n*	Female %	Average age (yr)	Average duration of illness (yr)	Average follow-up since DBS implantation (mo)	Target site
RCT	Luyten *et al*[20], 2016	24	50	39	NR	77	ALIC/BST
Non-RCT	Choudhury *et al*[78], 2017	1	100	45	21	51	ALIC
	Fayad *et al*[33], 2016	6	66	44.5	NR	92.5	VC/VS
	Graat *et al*[19], 2020	50	68	41.6	25.2	81.6	ALIC
	Gupta *et al*[35], 2019	2	100	46.5	23	42	VC/VS/ ALIC
	Greenberg *et al*[36], 2010	26	46	35.3	22	96	VC/VS
	Holland *et al*[21], 2020	9	44.4	40.2	NR	54.8	VC/VS
	Lee *et al*[37], 2019	5	60	32.4	16.2	49.8	ITP
	Mallet *et al*[22], 2019	14	42.8	43.8	NA	46	STN
	Polosan *et al*[38], 2019	12	67	38.3	18	38	STN
	Winter *et al*[28], 2021	6	33.3	39.6	18	72	ALIC/BNST

The study sample conducted by Fayad *et al*[33] corresponds to the follow-up of Goodman *et al*[16]'s study sample. Greenberg *et al*[36] conducted a multicenter study in which some patients from Fayad *et al*[33]'s study were included. The patients in the studies by Mallet *et al*[22] and Chabardes *et al*[29] are included in the STOC study. ALIC: Anterior limb on internal capsule; BNST: Bed nucleus of stria terminalis; ITP: Inferior thalamic peduncle; NR: Not reported; RCT: Randomized controlled trial; VC/VS: Ventral caudate/ventral striatum.

DBS has also been observed, which supports the relative independence of the antidepressant and antiobsessive effects[33,42].

Global functioning: Consideration of DBS for OCD presupposes the presence of extremely severe obsessive symptoms that severely impair patient function in all areas of life. The GAF was the most frequently used scale of functionality in the studies included, with median baseline scores of 40 indicating impairment in work or school, family relations, judgment, thinking, or mood[41]. Of the 40 studies analyzed, 23 included an assessment of global functioning as a secondary outcome, using the GAF scale, the Instrumental Activities of Daily Living scale, the Clinical Global Impressions Severity Scale, or the Social and Occupational Functioning Assessment Scale. All but one study reported a progressive and significant improvement in the functionality of patients with OCD after DBS treatment, which was maintained in parallel to their obsessive symptoms in the LT follow-up studies. However, the improvement was not always universal; some studies described the persistence of social difficulties despite an abrupt increase in the GAF scale in the first 24 mo[29]. In the only article to report no functional improvement, stimulation of the medial dorsal and ventral anterior nucleus of the thalamus did not produce any improvement in obsessive symptoms [45].

Adverse effects

The side effects of DBS can also be divided into surgical or hardware-related complications, stimulation-induced side effects, and others[46]. The first observable side effects are those related to the device implant; they are associated with the surgery or the presence of the electrodes in the brain, and are usually temporary. Some patients needed reoperation due to poor electrode positioning[19,44,45] or intracranial infection [36,39] enforcing removal and reimplantation[19,36], a situation that significantly increased the surgical risks. Intracranial hemorrhage was the most severe secondary

Table 6 Summary of results for the short-term studies

	Ref.	Average baseline Y-BOCS	Average Y-BOCS at LFU	Average Y-BOCS improvement (%)	Average responders (%)	Depression (HDRS, BDI, MADRS, DASS, POMS)	Depression scale improvement	Global functionality (GAF, CGIS, SOFAS)	Functionality improvement
RCT	Abelson *et al* [67], 2005	32.7	23	30	50	Yes, HDRS	Yes	NR	NR
	Barcia *et al* [32], 2019	32.2	15.4	51	85.7	Yes, HDRS and BDI	No	NR	NR
	Goodman *et al*[16], 2010	33.7	18	46	67	Yes, HDRS	Yes	Yes, CGISS	Yes
	Abelson *et al* [67], 2005	32.3	25.4	21	8.3	Yes, HDRS and BDI	Yes	Yes, GAF	Yes
	Barcia *et al* [32], 2019	36.1	14.1	61	NR	Yes, MADRS	Yes	NR	NR
	Goodman *et al*[16], 2010	33.5	23.2	30	37.5	Yes, MADRS	No	NR	NR
Non-RCT	Anderson and Ahmed [74], 2003	34	1	97	100	NR	NR	Yes, GAF	Yes
	Aouizerate *et al*[75], 2009	25	11	56	100	Yes, HDRS	Yes	NR	NR
	Azriel *et al* [76], 2020	33	16	48	100	NR	NR	NR	NR
	Chabardes *et al*[29], 2020	33.3	15.8	53	73	NR	NR	Yes, GAF	Yes
	Chang *et al* [77], 2017	36	25	30	0	Yes, HDRS	NR	Yes, GAF	Yes
	Coenen *et al* [79], 2017	30	20.5	31	50	Yes, BDI	Yes	Yes, GAF	NR
	Denys *et al* [44], 2020	33.7	20.2	40	52	Yes, HDRS	Yes	NR	NR
	Doshi *et al* [80], 2019	19	5	73.7	100	Yes, HDRS	Yes	NR	NR
	Farrand *et al* [42], 2018	32.8	24	26	42.8	Yes, DASS-D	Yes	Yes, SOFAS	Yes
	Franzini *et al* [81], 2010	34	20	41	50	Yes, HDRS	Yes	Yes, GAF	Yes
	Gabriëls *et al* [53], 2003	33.6	21	37.5	66.6	Yes, POMS	No	NR	NR
	Grant *et al* [34], 2016	32	9	71	100	NR	NR	NR	NR
	Huys *et al* [30], 2019	30.9	20.7	33	40	Yes, BDI	No	Yes, GAF	Yes
	Islam *et al* [40], 2015	35.3	20.8	41	50	Yes, HDRS	NR	Yes, GAF	NR
	Jiménez *et al* [55], 2013	35.8	15.5	56	100	NR	NR	Yes, GAF	Yes
	Maarouf *et al*[45], 2016	34.7	31	10	0	Yes, BDI	NR	Yes, GAF	No
	Menchón *et al*[13], 2021	34.7	20	42	60	Yes, MADRS	Yes	Yes, GAF	Yes
	Mulders *et al*[82], 2017	34	17	48	100	NR	NR	NR	NR

	Plewnia *et al* [83], 2008	31	24	25	0	NR	NR	Yes, GAF	Yes
	Roh *et al* [61], 2012	38	14.8	59.7	100	Yes, HDRS	NR	Yes, GAF	Yes
	Sachdev *et al* [84], 2012	39	5	87.1	100	NR	NR	NR	NR
	Senova *et al* [85], 2020	31	1	96	100	Yes, MADRS	Yes	NR	NR
	Tsai *et al* [49], 2012	36.3	24	33.8	25	Yes, HDRS	Yes	Yes, GAF	Yes

BDI: Beck depression inventory; CGISS: Clinical global impression severity scale; DASS-D: Depression anxiety stress scale-depression; GAF: Global Assessment of Functioning; HDRS: Hamilton depressive rating scale; LFU: Last follow-up; MADRS: Montgomery Asberg Depression rating scale; NR: Not reported; POMS: Profile of mood states; RCT: Randomized controlled trial; SOFAS: Social and Occupational Functioning Assessment scale; Y-BOCS: Yale-Brown Obsessive Compulsive scale.

Table 7 Summary of results for the long-term studies

	Ref.	Average baseline Y-BOCS	Average Y-BOCS at LFU	Average Y-BOCS improvement (%)	Average responders (%)	Depression (HDRS, BDI, MADRS, QIDS, IDS-30)	Depression scale improvement	Global buncionality (GAF, IADL, SF-36)	Functionality improvement
RCT	Luyten *et al* [20], 2016	35	19.3	45	67	Yes, HDRS	Yes	Yes, GAF	Yes
Non-RCT	Choudhury *et al*[78], 2017	37	21	43	100	Yes, BDI	Yes	Yes, IADL	Yes
	Fayad *et al* [33], 2016	33.6	15.1	55	66	Yes, HDRS	No	Yes, SF-36	Yes
	Graat *et al* [19], 2020	33.3	20.5	39	50	Yes, HDRS	Yes	Yes, GAF	Yes
	Gupta *et al* [35], 2019	38	11	71	100	Yes, BDI	Yes	NR	NR
	Greenberg *et al*[36], 2010	34	21.5	36	61	Yes, HDRS	Yes	Yes, GAF	Yes
	Holland *et al* [21], 2020	34.5	20.7	40.3	22	Yes, HDRS, MADRS, QIDS, IDS-30 and BDI	Yes	Yes, GAF	NR
	Lee *et al*[37], 2019	35	16	54	100	Yes, HDRS	Yes	NR	NR
	Mallet *et al* [22], 2019	32.4	15.4	50	75	Yes, BDI	Yes	Yes, GAF	Yes
	Polosan *et al* [38], 2019	34.3	20	41	NR	NR	NR	NR	NR
	Winter *et al* [28], 2021	32.1	17.7	45	66	Yes, BDI	Yes	NR	NR

BDI: Beck depression inventory; GAF: Global Assessment of Functioning; HDRS: Hamilton depressive rating scale; IADL: Lawton instrumental activities of daily living scale; IDS-30: Inventory of depressive symptomatology; LFU: Last follow-up; MADRS: Montgomery Asberg Depression rating scale; NR: Not reported; QIDS: Quick inventory of depressive symptomatology; RCT: Randomized controlled trial; SF-36: Short form survey; Y-BOCS: Yale-Brown Obsessive Compulsive scale.

effect related to surgery. Although its frequency was very low in most studies[13,22], in others[20,36] rates were as high as 4.8% or 7.7%. Seizures have been described during both ST follow-up[13,36,40] and LT follow-up after 2-5 years[20], with poor electrode positioning[13], intracranial infection[40], somatic complications (*e.g.*, hypoglycemia), and abrupt changes in the stimulation parameters cited as risk factors [40].

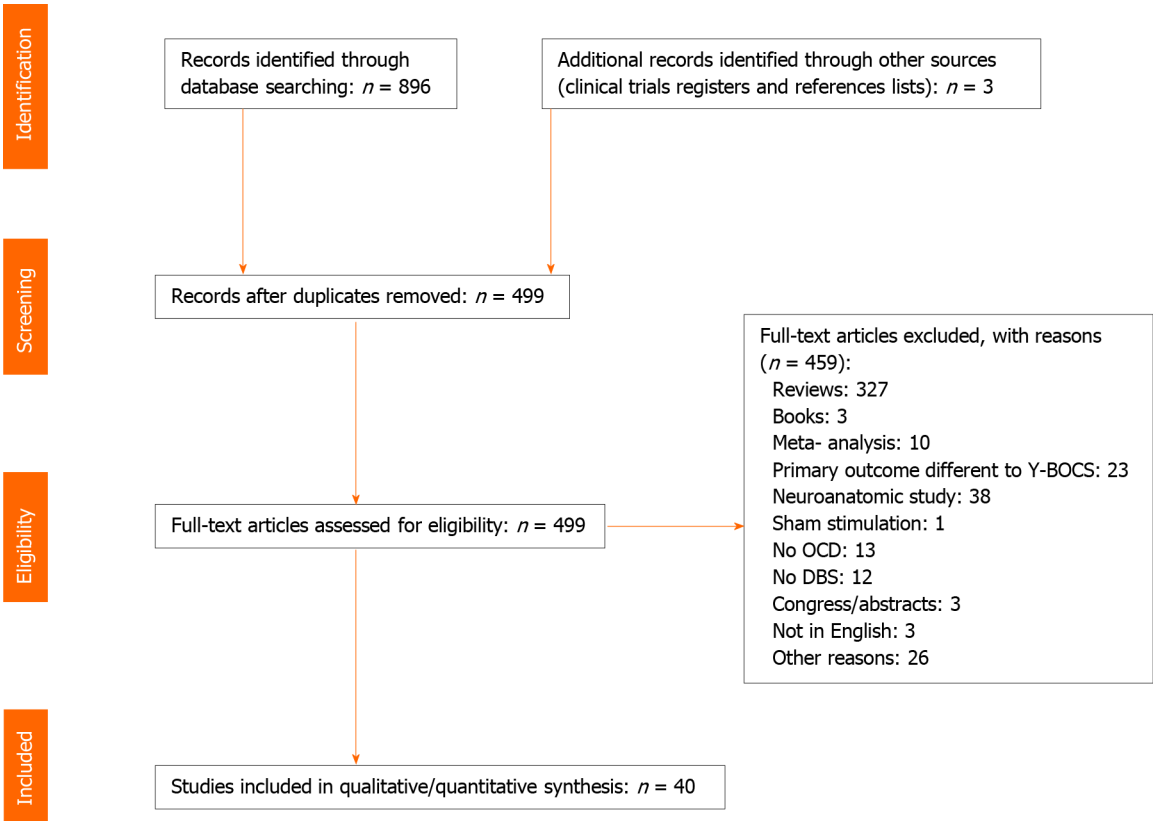


Figure 1 PRISMA flow diagram for add-on deep brain stimulation and obsessive-compulsive disorder in PubMed, Cochrane, Scopus databases and ClinicalTrials.gov databases. DBS: Deep brain stimulation; OCD: Obsessive-compulsive disorder; Y-BOCS: Yale-Brown Obsessive-Compulsive scale.

The most frequent side effect of stimulation is hypomania[21,22,43], although this usually resolves after adjusting the stimulation parameters[16,47,48]. Hypomania has been reported to be a predictor of good response to DBS in other studies, and this has confused the perceptions of its relevance as a side effect[48,49]. Denys *et al*[44] attributes the occurrence of hypomanic symptoms to the stimulation of the anterior limb of the internal capsule (ALIC) and argues that they should be considered not as an adverse effect but as a sign of effective treatment. However, the predictive utility of hypomania is controversial, because other authors have reported that it occurs equally in DBS responders and non-responders[44]. Indeed, the risk of manic and hypomanic symptoms may be modulated by clinical factors, with right monopolar stimulation and female sex predicting manic symptoms during DBS[50,51]. Other adverse effects related to stimulation include insomnia or sleep disturbances[16,33], weight gain[19], fatigue, subjective cognitive problems[19,52], and increased anxiety. Despite subjective reports of cognitive complaints, studies specifically addressing neuropsychological performance have detected no significant impact of DBS[16,20,53].

The relationship between DBS and the risk of suicide attempts or suicide is also controversial. Suicide may be related to the disease itself, to the DBS, or to the ineffectiveness of the treatment. Fernández de la Cruz *et al*[54] reported that patients with severe OCD symptoms were more likely to present suicide attempts (odds ratio = 5.45) and die from suicide (odds ratio = 9.83), and that a history of prior suicide attempt was the strongest predictor. Most studies associate suicide attempts or suicide after DBS in patients with OCD to a comorbid diagnosis of major depressive disorder[19,28,29] or to a lack of response to DBS and the persistence of disabling symptoms[19,20,29]. Comorbidities, including drug use and personality disorders, also appear to increase the risk of death by suicide during DBS among patients with OCD[22,55]. Finally, Graat *et al*[19] reported death by euthanasia in two nonresponding patients with no history of suicide attempts and an average of 4.5 years from DBS implantation to death.

We found no significant differences in these adverse effects between the ST and LT studies.

Predictors of response

DBS is not only expensive but also poses the risk of severe side effects. Given the risks involved, the significant consumption of human and clinical resources, and the need for lifelong follow-up, establishing reliable predictors of response would help to improve patient selection, guide DBS implantation, and optimize stimulation parameters. To date, however, no clinical variables or biomarkers have been clearly defined, probably because of the heterogeneity of the neuroanatomical targeting, the electrodes used, and the stimulation protocols.

Clinical variables: Few published studies have addressed the existence of clinical predictors of response to DBS. Among those that have, most have failed to uncover any clear predictive factors. In the study by Huys *et al*[30], gender, age, preoperative severity (Y-BOCS score), and personality traits did not predict patient improvement after DBS. Similarly, Chabardes *et al*[29] detected no significant differences by age at OCD onset, age at surgery, disease duration, or obsession and compulsion types between responders and nonresponders after 24 mo of subthalamic nucleus (STN)-DBS; however, they detected a significantly higher female-to-male ratio in the responder group, with all females meeting the response criteria. Nevertheless, contradictory results have been reported for age at OCD onset. In a meta-analysis of 16 studies Alonso *et al*[9] reported that patients with later onset OCD exhibited higher response rates and greater Y-BOCS reductions, whereas Mallet *et al*[22] found that patients with early onset OCD showed better LT outcomes after 46 mo of STN-DBS. In another meta-analysis, Martinho *et al*[10] observed that illness duration positively predicted ST response in RCTs, but not LT response in the open phases of those studies. Illness severity at baseline did not predict ST response, but it negatively predicted response at the last follow-up.

Differences in response to DBS between specific symptom profiles have also been hypothesized, as occurs with selective serotonin reuptake inhibitors and CBT. Intuitively, this is highly probable in a focal neuromodulating tool like DBS in which the different symptom dimensions of OCD are reported to have partially distinct neural substrates[56]. Nevertheless, the data on this topic are scarce and often contradictory. Many published trials lack detailed descriptions of symptom profiles and no single study has used a specific psychometric tool to assess OCD symptom dimensions. Two of the ten patients in the study by Greenberg *et al*[57] who had the poorest response to ventral caudate (VC)/ventral striatum (VS) DBS suffered OCD symptoms motivated principally by a feeling of incompleteness and a need to repeat actions until they felt that everything was "just right". Nevertheless, four other patients who also reported "just right" experiences significantly improved with DBS. Patients with contamination and washing symptoms showed lower response to DBS (45.5%) than those who suffered doubts and checking compulsions (100%).

According to Denys *et al*[43], patients needing perfection, symmetry, or reassurance, as well as those with hoarding, showed poor response to nucleus accumbens (NAcc) stimulation. In other series[49,58-61], patients with symmetry or ordering obsessions and compulsions have been reported to respond to DBS. Results for hoarding symptoms are also controversial. Welter *et al*[39] described that hoarding was the main symptom in one of two patients resistant to DBS of the STN, NAcc, and caudate nucleus; by contrast, Fontaine *et al*[62] reported that prominent hoarding symptoms almost disappeared after STN stimulation in a patient with Parkinson's disease, while Guehl *et al*[60] described a woman with hoarding, contamination/cleaning, and symmetry/ordering symptoms who improved significantly with caudate nucleus stimulation. Similarly, some authors have reported that somatic obsessions improve with DBS[59], but others have not[53]. In the meta-analysis by Alonso *et al*[9], it was notable that the presence of sexual or religious obsessions and compulsions was associated with a better response.

Interestingly, two recent studies by Barcia *et al*[32,63] raise the possibility of personalizing the targets in DBS in patients with OCD depending on the obsessional focus. They stimulated seven patients with OCD by placing a tetrapolar electrode along the striatum and observed that those with mainly washing obsessions and compulsions responded better to the more ventral contacts, while those presenting checking, ordering, and incompleteness symptoms responded better to activation of the more dorsal contacts. The authors concluded that the most effective neuroanatomical target structure for each patient could be calculated by combining a preoperative index derived from functional MRI symptom provocation and probabilistic tractography.

Electrode location, intraoperative changes and electrophysiological data: Haq *et al*[48] first reported that patients who showed higher percentages of laughing conditions

(smiling or laughter with euphoria) during intraoperative DBS testing for electrodes placed at the ALIC and NAcc showed the greatest reduction in Y-BOCS scores in the LT. Similarly, Tsai *et al*[49] reported that the appearance of smiling/Laughter on postoperative test stimulations performed two weeks after implantation at the VC/VS also significantly predicted good response in the LT (at 15 mo). Goodman *et al*[16] reported that experiencing hypomania as an early stimulation-induced side effect made clinical response more likely. Hypomania is the most frequent side effect of DBS programming in OCD and is reported to affect 40%-45% of subjects[44,50], but it remains unclear whether it necessarily predicts a good response to DBS in OCD.

Optimal electrode location is an anatomical factor that markedly affects response to DBS. Current targets in OCD include the ALIC, the VS, the anteromedial limbic STN, and midbrain. These four targets affect orbitofrontal cortex (OFC) or anterior cingulate cortex (ACC) connections passing through, entering, or leaving the internal capsule. This explains why stimulation at different brain locations can target different components of the same circuit. To optimize outcomes, the initial electrode position within the ALIC has changed over the years; several studies have concluded that more posteriorly targeted stimulation at the bilateral bed nucleus of the stria terminalis and the VC/VS near the ACC appears to improve outcomes, producing greater symptom reduction than more dorsal or anterior stimulation of the ALIC[13,20,36] or NAcc[40]. Although most studies indicate that differences between targets in relation to the antiobsessive effect of DBS are not significant, the different electrode locations do produce specific effects: For example, DBS of the anteromedial STN, but not the VC/VS, improves cognitive flexibility, while DBS of the VC/VS achieves greater mood improvement than STN stimulation[17].

Regarding electrophysiological measures, Welter *et al*[64] reported a correlation between presurgical STN neuronal activity and response to bilateral high-frequency STN stimulation. Good response was associated with higher mean presurgical neuronal discharges, bursts, and intraburst frequencies, but with lower mean presurgical interburst intervals. van Westen *et al*[65] replicated these findings and reported that patients with lower interburst intervals and higher intraburst frequencies had the best Y-BOCS outcome.

Neuroimaging data: With respect to neuroimaging data, in a small sample (six patients) Van Laere *et al*[66] found that higher preoperative activity in the subgenual ACC assessed by positron emission tomography with fluorodeoxyglucose integrated with computed tomography (^{18}F-FDG PET/CT) correlated with greater response to DBS. Abelson *et al*[67] reported that such scans detected decreased OFC activity in only two of four patients who responded to bilateral ALIC stimulation, suggesting that DBS improves OCD symptoms only when it restores the inhibitory function of the ventral cortico-striato-thalamo-cortical pathway. Le Jeune *et al*[68] similarly reported a reduction in Y-BOCS after DBS that correlated with decreased metabolic activity in the ventro-medial prefrontal region of the OFC. Regarding connectivity, Figee *et al*[69] detected that clinical improvement after DBS correlated with a normalization of functional connectivity in the NAcc prefrontal cortex, and Baldermann *et al*[70] recently showed that response to DBS could be predicted by analyzing the effects of stimulation on structural connectivity to prefrontal and frontal regions. Modulation of structural connectivity to the right middle frontal gyrus with DBS was associated with a better clinical response in a sample of six patients, whereas changes in connectivity to the OFC were associated with nonresponse. The same group has recently reported that response to ALIC and STN in four OCD cohorts predicted whether electrodes could or could not stimulate a fiber bundle connecting medial prefrontal regions to the STN[71].

DISCUSSION

In this study we aimed to summarize the efficacy and tolerability of DBS for treatment-resistant severe OCD, comparing ST and LT response to stimulation, and assessing whether different patterns and predictors of response emerged from the data available from 40 studies including a total of 344 patients. Of these, 29 studies (with 230 patients) covered ST response over an average of 18.5 mo, and 11 studies (with 155 patients) covered LT response over an average of 63.7 mo. The mean decreases in Y-BOCS scores from baseline to final follow-up were 47.4% in the ST studies (Y-BOCS fell from 33 to 17.2) and 47.7% in the LT studies (Y-BOCS fell from 34.4 to 18). The percentage of responders increased from 60.6% in the ST studies to 70.7% in the LT

studies, indicating that DBS provided effective therapy for severe resistant OCD in at least two-thirds of subjects in the long term, comparable with data published in previous meta-analyses[9-11]. Our results suggest that the first year of stimulation is critical to obtaining benefit from DBS. Three patient groups could be described according to their pattern of LT response to DBS: sustained good responders (49.5%), persistent non responders (resistant patients with no or almost no improvement) despite treatment adjustments (28.1%), and fluctuating responders who presented relapses of their symptoms irrespective of environmental factors (22.5%). At this point no clear predictors of response can be established, in terms of either clinical features or biomarkers.

Although DBS in OCD is far less effective than in neurological disorders such as essential tremor, its therapeutic potential should not be overlooked if we consider that candidates for DBS have typically proven treatment-resistant. Indeed, they usually show no improvement with multiple pharmacological approaches, including all selective serotonin reuptake inhibitors, clomipramine, and various antipsychotics, as well as prolonged and intensive CBT. The fact that two-thirds of these severely disabled and highly resistant patients improve on DBS supports the efficacy of direct electrical modulation of hypothesized dysfunctional circuits in OCD. Along these lines, recent proposals to individualize anatomical targets by brain connectivity findings or symptoms hold out promise for future improvements[32].

The results of published studies are limited to adult patients with OCD. Candidates for DBS must meet strict criteria in order to be considered for electrode implantation: their Y-BOCS scores must indicate severe to extreme OCD and they must present serious impairment in daily functioning lasting more than five years despite a minimum of three adequate pharmacological trials and cognitive-behavioral therapy. Even for patients with early-onset OCD in childhood or adolescence, it takes years to meet these criteria. In fact, in the studies assessed here mean illness duration before DBS implantation was around 24 years. It is unknown at this time if younger patients or patients with shorter disease progression might be better candidates for DBS.

What can be offered to patients with treatment resistance or limited/fluctuating response to DBS? Several studies indicate the usefulness of retrying CBT after implanting electrodes in order to target rituals that persist even though patients experience fewer intrusive thoughts or less associated emotional distress[19]. In these cases, the rituals may have been a part of their lives for years and may have become habitual. For subjects resistant to DBS, especially those in whom suboptimal electrode placement is confirmed, reimplantation of the electrodes at different targets may be appropriate. There are some reports of cases that have been successfully managed in this way, in spite of the surgical risks [19]. Studies in which more than two electrodes are implanted in the same patient, allowing the stimulation of limbic and non-limbic areas, suggest that some subjects respond to the stimulation of certain anatomical targets but not others, even though these features share the cortico-striato-thalamo-cortical pathway. Finally, subjects who exhaust all DBS options should still be considered for stereotactic surgery. Neuroablative surgical techniques have improved dramatically in recent years, showing optimized results and reduced side effects[72]. In a recent meta-analysis, ablative neurosurgery for OCD obtained a greater reduction in Y-BOCS scores than DBS (50.4% *vs* 40.9% reductions) and also produced fewer adverse effects (in 43.6% *vs* 64.6% of patients)[73].

DBS is not without adverse effects. Although most are mild and transient, and can usually be resolved by modifying the stimulation parameters, some serious adverse effects are possible. Among the psychiatric effects, hypomania was the most commonly identified in the present review, but it remains unclear whether this is a predictor of DBS response or an inevitable consequence of the treatment's mechanism of action. Another topic that deserves special attention is the risk of suicide and death by suicide among patients with OCD who are treated with DBS. Most studies relate this risk to the presence of comorbid major depressive disorder or the absence of an adequate response to DBS[19,29]. The presence of excessive and unrealistic expectations of improvement after stimulation also seems to increase the risk of suicidality [13]. It is therefore essential that patients receive clear and realistic information about their expected response to DBS and are aware that several months of treatment and multiple adjustments are often necessary before an adequate response is achieved. Careful ongoing assessment of suicide risk is required, especially in the presence of comorbid major depressive disorder and nonresponse.

To date, it has not been possible to establish clear predictors of response to DBS that might help to improve patient selection or treatment application. In fact, the significant heterogeneity in the targets proposed for stimulation and the absence of standardized programming settings have meant that DBS has remained an experimental therapeutic

option for OCD, with limited scientific proof of its efficacy. Recent efforts to develop measurable biomarkers using fMRI, tractography, or electroencephalography may help to develop a more personalized approach to DBS, and thus identify more accurately the patients most likely to benefit from a treatment with a very high economic cost and significant risks.

Our review has several limitations. We decided not to restrict our search to RCTs and included open studies, series, and published clinical cases, which represented 79% of ST studies and 91% of LT studies. Although this makes our results more representative, it also limits their methodological validity because we were unable to adequately control for biases and for the risk of a placebo response. The marked heterogeneity among the studies reviewed, including sample size, study design, stimulation parameters, anatomical targets, and psychometric tools for defining primary and secondary outcomes, also makes any meaningful comparison difficult. Finally, many groups use other therapeutic approaches (*e.g.*, CBT) concurrently with DBS or do not define whether pharmacological treatments are interrupted after DBS implantation. Therefore, we cannot be sure that the beneficial effects attributed to DBS were not in fact due to a multimodal treatment approach.

CONCLUSION

In conclusion, the present review confirms that DBS is a promising therapy for patients with severe resistant OCD, with evidence of efficacy in the short and long term. There remain many unknowns, including the optimal anatomical targets, the criteria for standardized stimulation protocols, and the identification of biomarkers or factors that predict outcomes and allow treatment individualization. To achieve a progressive improvement of DBS outcomes, we strongly recommend that this approach be applied only at centers that can guarantee access to multidisciplinary teams comprising not just neurosurgeons with experience in functional surgery but also psychiatrists and behavioral therapists with adequate expertise in the pharmacological and psychotherapeutic management of severe OCD. This strategy will ensure the selection of suitable potential candidates, the timely implementation of advances in surgical techniques, improved postoperative management, optimization of stimulation parameters, and the concomitant use of other therapies like CBT. The development of an international registry with clinical, programming, and neuroimaging data on all patients undergoing DBS for treatment-resistant OCD would also contribute to expanding our knowledge of this technique, which constitutes the last therapeutic option for many patients with severe OCD.

ARTICLE HIGHLIGHTS

Research background

Twenty years after the first deep brain stimulation (DBS) implantation in a patient with obsessive-compulsive disorder (OCD), we review all the information published to date regarding the efficacy and tolerability of this therapeutic option for severe obsessive patients resistant to pharmacological approaches and behavioral therapy.

Research motivation

There are still many unknowns regarding the benefits and risks of using DBS in OCD. The main ones are the optimal anatomical targets, the best stimulation parameters, the long-term effects of the therapy or the possibility of establishing clinical or biological factors associated with response. Responding to them would allow optimizing the results of this therapeutic alternative, with a high economic and human resources cost, and not without potentially serious risks.

Research objectives

The main objectives of this systematic review were to summarize existing knowledge regarding efficacy and tolerability of DBS in treatment-resistant OCD as well as to analyze the possible existence of response predictors that allow improving the selection of candidates. We confirmed that DBS proved to be an effective and safe alternative for two out of three severe and resistant OCD patients who received it. Although we did not detect any clear predictor of response, there are promising proposals based on the use of neuroimaging tools to individualize treatment that

should be analyzed in depth in future research.

Research methods

We performed a comprehensive search in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020 with "(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS)" as searching strategy. Inclusion criteria were a main diagnosis of OCD, DBS conducted for therapeutic purposes in humans and variation in symptoms of OCD measured by the Yale-Brown Obsessive-Compulsive scale (Y-BOCS) as primary outcome. Data was recorded using a standardized collection tool and analyzed with descriptive statistics. Risk of bias was assessed using the Cochrane Handbook for Systematic Reviews of Interventions for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies.

Research results

Our systematic review detected 40 studies fulfilling inclusion criteria. 29 of them reported results on short-term response to DBS in 230 patients (follow-up: 18.5 ± 8 mo, range: 7-36) and eleven on long-term response in 155 subjects (63.7 ± 20.7 mo, range: 38-96). Mean Y-BOCS reduction reported on short-term studies was 47.4% ± 21% and on long-term studies 47.2% ± 9.9%, confirming the long-term stability of the response. A significantly greater number of patients fulfilled criteria for response (Y-BOCS reduction > 35%) on the long-term studies (70.7%) than in the short-term ones (60.6%), although the maximum symptom reduction was achieved in general in the first 12-14 mo after DBS implantation. Comorbid depressive symptoms tend to improve in parallel to obsessive symptoms, although this correlation was not observed in all patients. DBS was well-tolerated by most OCD patients, with reversible hypomania as the most frequently reported side effect associated to stimulation. No clear clinical or biological predictors of response emerged from our data, probably due to the high heterogeneity on DBS application conditions in OCD patients.

Research conclusions

Our results underscore the importance of exploring new strategies that allow individualizing the conditions of application of DBS in OCD, combining neuroimaging data and a detailed analysis of the patient's symptoms.

Research perspectives

Future directions on research on DBS application in OCD should focus on establishing which individual factors at the clinical and/or neuroimaging level can allow us to establish which will be the target and the optimal stimulation conditions for each patient, since the results show that although the standard application of the technique is effective and safe for 2 out of 3 operated patients, there are still patients who do not benefit from the treatment.

ACKNOWLEDGEMENTS

We thank the CERCA programme/Generalitat de Catalunya for institutional support.

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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 October 19; 11(10): 681-914



Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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Monthly Volume 11 Number 10 October 19, 2021

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INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xu Guo*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
October 19, 2021

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ONLINE SUBMISSION
https://www.f6publishing.com

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E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Psychiatry

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World J Psychiatr 2021 October 19; 11(10): 681-695

DOI: 10.5498/wjp.v11.i10.681

ISSN 2220-3206 (online)

FRONTIER

Framework for internal sensation of pleasure using constraints from disparate findings in nucleus accumbens

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Author contributions: Vadakkan KI conceived the idea, drew the figures and wrote the manuscript.

Conflict-of-interest statement: United States patent number 9477924 pertains to an electronic circuit model of the inter-postsynaptic functional LINK.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Canada

Peer-review report's scientific quality classification

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Abstract

It is necessary to find a mechanism that generates first-person inner sensation of pleasure to understand what causes addiction and associated behaviour by drugs of abuse. The actual mechanism is expected to explain several disparate findings in nucleus accumbens (NAc), a brain region associated with pleasure, in an interconnected manner. Previously, it was possible to derive a mechanism for natural learning and explain: (1) Generation of inner sensation of memory using changes generated by learning; and (2) Long-term potentiation as an experimental delayed scaled-up change by the same mechanism that occur during natural learning. By extending these findings and by using disparate third person observations in NAc from several studies, present work provides a framework of a mechanism that generates internal sensation of pleasure that can provide interconnected explanations for: (1) Ability to induce robust long-term depression (LTD) in NAc from naïve animals; (2) Impaired ability to induce LTD in "addicted" state; (3) Attenuation of postsynaptic potentials by cocaine; and (4) Reduced firing of medium spiny neurons in response to cocaine or dopamine. Findings made by this work are testable.

Key Words: Pleasure; Internal sensation; Mind; Memory; Long-term potentiation; Long-term depression; Nucleus accumbens; Drug addiction

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Core Tip: Pleasure has been studied by examining animal behaviour and its correlations with molecular and electrophysiological changes. Drugs of abuse generate pleasure along with several seemingly unrelated changes in nucleus accumbens (NAc). When pleasure was examined as a first-person inner sensation, it was possible to arrive at a framework of a causal mechanism for its generation that can also provide inter-

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 3, 2021
Peer-review started: May 3, 2021
First decision: June 17, 2021
Revised: June 27, 2021
Accepted: September 2, 2021
Article in press: September 2, 2021
Published online: October 19, 2021

P-Reviewer: Onaolapo AY
S-Editor: Fan JR
L-Editor: A
P-Editor: Guo X

connected mechanistic explanations for long-term depression (LTD) in NAc in naïve animals, impaired ability to induce LTD in addicted state, attenuation of postsynaptic potentials by both cocaine and dopamine, and reduced firing of medium spiny neurons in NAc by dopamine. Findings made by this work are testable.

Citation: Vadakkan KI. Framework for internal sensation of pleasure using constraints from disparate findings in nucleus accumbens. *World J Psychiatr* 2021; 11(10): 681-695
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/681.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.681

INTRODUCTION

Around 269 million people used drugs of abuse in 2018 and nearly 35.6 million people suffer from drug use disorders globally[1]. Since drugs provide internal sensation of pleasure to which users can get addicted, it is necessary to understand the basic mechanism that generates pleasure and possible ways this leads to addiction. Current studies of brain functions such as perception, memory, fear, anxiety, pleasure, hunger, thirst, reward, aversion, and pain are carried out in animal models by examining behavioural motor actions indicative of those brain functions. During these examinations, there is an implicit assumption that nervous system generates internal sensations of each of those brain functions concurrently with behaviour. Studies have found correlations between behavioural motor actions and sets of neurons that fire and/or their firing rates in brain regions that have a predominant role in those brain functions. In addition, correlations are also found between behaviour and electrophysiological findings in those brain regions. To understand how the brain operates to generate inner sensations of each of the above brain functions, an interconnected framework of explanations is necessary. Even though it is not possible to directly test formation of first-person properties of inner sensations of a brain function, a first step will be to derive plausible mechanisms for their generation using constraints from several disparate findings associated with each brain function.

Learning is expected to generate testable changes that are used for generating first-person inner sensations of memory. By examining fine details of neuronal processes and their properties, it was possible to arrive at a learning mechanism from which inner sensations of memory can be retrieved[2,3]. A summary of the basis of derivation is as follows. Examination of a neuron having thousands of input terminals shows that subsets of nearly 140 input signals can fire that neuron[4,5]. Since input signals attenuate as they propagate towards neuronal soma, it is possible that even a small fraction of one input can fire a neuron, which is being held at a sub-threshold activation state short of that input fraction[6,7]. Associative learning between two stimuli (stimulus 1 and 2) is expected to take place at a location where signals from these stimuli converge. This led to searching for a specific location where learning can generate a specific physical change in millisecond timescales that can be retained for different durations and then enable a cue stimulus (either stimulus 1 or 2 or their components) to generate inner sensation of memory of the second stimulus to explain working, short-term and long-term memories[3].

Input terminals of a neuron are the dendritic spines (spines or postsynaptic terminals) that synapse with output terminals of many neurons in the previous neuronal order. Mean inter-spine distance between spines on the dendrite of a pyramidal neuron is more than the mean spine head diameter[8]. Hence, spines that are abutted to each other most likely belong to different dendrites. Electron microscopic views of cerebral cortex show abutted neuronal processes (including spines) with very minimal extracellular matrix (ECM) space between them. To satisfy requirements of classical conditioning paradigm, interactions between spines that belong to different neurons are necessary[3,9]. This led to the derivation of inter-postsynaptic (inter-spine) functional LINKs (IPLs) between spine heads that belong to different neurons as a general structural change taking place within milliseconds during learning. At a later time when one of the cue stimuli reactivates an IPL, it can depolarize the "inter-LINKed" second spine from a lateral direction. Head region of this inter-LINKed spine gets strongly depolarized during the intermittent arrival of action potentials at its presynaptic terminal when signals from a sensory stimulus

arriving from the environment reach that presynaptic terminal. Head regions of all the spines including the inter-LINKed spines are continuously getting depolarized by the quantal release of neurotransmitter molecules from their corresponding presynaptic terminals, even during sleep. These impart a dominant state that depolarization of a spine results from its presynaptic terminal. Such dominant states of spines of neurons from different neuronal orders can provide a dominant system state that activation of a spine occurs from a stimulus arriving from the environment and that activation of a specific set of spines occurs from arrival of a specific stimulus. In this context, a theoretical possibility is that any instantaneous depolarization of a spine from a lateral direction through an IPL can generate a hallucination (internal sensation of a stimulus in its absence) at the inter-LINKed spine about specific sensory features of the associatively learned second stimulus as a system property[3,9] (Figure 1). This is anticipated of a mechanism that generates memory in the nervous system[10]. This hypothesis called semblance hypothesis is found to agree with the constraints offered by a large number of findings from multiple levels of the system[9].

Ability to induce long-term potentiation (LTP) at a location can be regarded as resulting from the formation of IPLs between abutted spines of different neurons at that location that receive converging excitatory inputs[11]. Since (1) Membrane segments from intracytoplasmic vesicles that carry α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) subunits can re-organize the cell membrane of lateral spine head region; (2) GluR1 AMPAR subunits are located up to 25 nm beyond the synaptic margin[12], an ideal location for inter-spine interactions; and (3) Endocytosis of GluR1 AMPAR vesicles that uses fragments of membranes from lateral spine head regions is associated with a reversal of LTP (LTP decay)[13] that can be scaled-down to explain the reversal of formed IPLs as a mechanism for physiological forgetting, IPL formation can be viewed as a suitable change triggered by learning[9]. Since (1) Dopamine has a role in motivation-related associative learning [14]; (2) Dopamine lead to the persistence of one-trial hippocampus-dependent memory[15]; and (3) Dopamine cause spine enlargement[16], release of dopamine is expected to augment inter-spine interactions leading to IPL formation and facilitate learning in a motivated state[9].

Application of energy of a different configuration than that is necessary to induce LTP generates long-term depression (LTD) in specific brain regions. An example of such a location is nucleus accumbens (NAc), a brain region associated with generation of pleasure. Cellular changes following LTD stimulation lead to depression of net excitatory postsynaptic potentials recorded from the recording electrode. Since energy is required for stimulation, LTD is an active process and not mere reversal of a mechanism responsible for the decay of LTP[13]. Since experimental results show that it takes several minutes for LTD induction[17,18], it indicates that LTD induction involves time-dependent cellular changes similar to that of LTP induction[11]. Hence, it is necessary to explain time-dependent changes occurring at specific locations where LTD can be induced. Similar to LTP, LTD in the hippocampal synaptic areas is implicated in different types of learning[19-22]. Necessity for stimulation energy and significant delay for induction of LTD following stimulation indicate that several IPLs are formed during LTD induction, similar to that occur during LTP induction[11]. To understand the mechanism that generates internal sensation of pleasure, it is necessary to (1) Examine the neuronal connections to NAc; (2) Examine conditions that allow experimental induction of LTD at this brain region; and (3) Use constraints from all the findings at this region to derive a mechanism for internal sensation of pleasure that can be inter-connected with the remaining findings.

NAc CONNECTIONS

Studies have shown that NAc is primary site mediating reward behaviour and is associated with both reinforcing and addictive behaviours in response to drug use. 95% of cells in the NAc are medium spiny neurons (MSNs). MSNs are called “spiny” due to the abundance of spines on their dendrites. However, visual examination of patterns of distribution of spines on these MSNs[23,24] shows that mean inter-spine distance is comparable to that of the mean spine diameter, which almost matches with the finding in pyramidal neurons that mean inter-spine distance is more than the mean spine diameter[8]. Electron microscopic images of NAc show negligible ECM between cellular processes in many locations[25,26]. Hence, it is possible to infer that the nearest spine to one spine on the dendrite of an MSN is a spine on a different dendrite, which most likely belongs to a different neuron or occasionally to the same neuron.

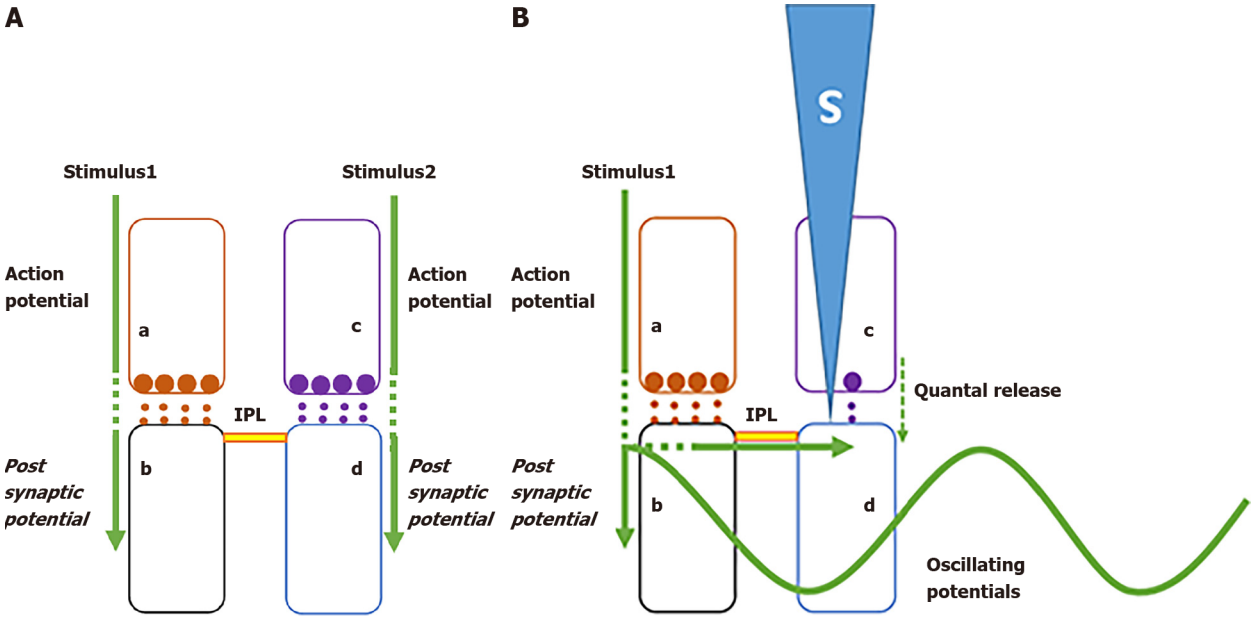


Figure 1 Generation of internal sensation of memory which is used as a reference mechanism to examine internal sensation of pleasure. A: During associative learning between stimulus 1 and 2, signals from these stimuli propagate towards converging locations where inter-postsynaptic functional LINKs (IPLs) between postsynaptic terminals (spines) b and d occur. Spines b and d are depolarized intermittently when action potentials arrive at their presynaptic terminals a and c respectively, and the head regions of these spines are continuously being depolarized by quantally-released neurotransmitter molecules from their presynaptic terminals. These provide a dominant state that a spine is depolarized by its presynaptic terminal that in turn receive signals from stimuli from the environment and is a necessary background condition for generating internal sensation of memory; B: In the above mentioned background state, arrival of stimulus 1 reactivates IPL b-d to cause an incidental lateral activation of postsynaptic terminal d to spark a cellular hallucination (shown using a blue triangle marked S inside) of a sensory stimulus arriving from the environment through its presynaptic terminal c. Details of the method by which sensory qualia of semblions can be determined was described previously[3]. This matches with the expectation of a mechanism for memory[10]. Waveform: Synaptic transmission through synapse a and b and propagation of depolarization through IPL b-d contribute vector components of oscillating extracellular potentials whose frequency needs to be maintained in a narrow range for inducing internal sensation of memory. Specific electrophysiological findings in locations where sensory stimuli converge were found to correlate with behavioural motor actions indicative of specific brain functions. Long-term potentiation (LTP) that can be induced at locations where sensory stimuli converge is an example[87,88]. After application of a high-energy stimulus at a region rich in synapses and following a delay of at least 20 to 30 s[89,90], application of a regular stimulus at the same location generates a potentiated effect when recorded from the postsynaptic dendritic region or postsynaptic neuronal soma. Ability to induce LTP has shown several correlations with animals' ability to learn. It was possible to explain how learning-induced formation of IPLs is artificially produced in a delayed scaled-up manner during experimental LTP induction[11]. By keeping correlation between the ability to generate internal sensation of memory that matches with sensory features of the item whose memory is retrieved and the ability to induce LTP at specific locations[11], specific electrophysiological changes that can be induced at these locations can be examined to arrive at a mechanistic explanation for internal sensation of pleasure. Since there are specific electrophysiological changes that can be induced at locations responsible for different brain functions, a comparative examination can be carried out to understand how different internal sensations are generated (modified from[3]).

Several studies in addiction research have examined changes in synapses on the spines of MSNs in NAc[27-30]. Spines on the dendrites of MSNs receive excitatory inputs from hippocampus, amygdala, thalamus and medial prefrontal cortex. Separate set of spines of MSNs receives inhibitory inputs from ventral tegmental area (VTA) (Figure 2). Dopaminergic inputs from the VTA form additional synapses with the heads or necks of spines that synapse with excitatory inputs[31]. In striatum, certain dopamine functions necessitate spatiotemporal precision between dopamine release sites and receptor locations[32]. It is necessary to find how these connections are related to the generation of internal sensation of pleasure and the ability to generate experimental LTD in NAc.

KEY FINDINGS IN NAc THAT NEED INTERCONNECTED EXPLANATIONS

There are several disparate findings in NAc. Major requirement to understand the mechanism by which pleasure is generated is to reach a single mechanism that can provide inter-connected explanations for all those findings. Constraints offered by all the findings together provide an opportunity to derive a unique solution (Table 1).

Table 1 Key findings in nucleus accumbens and constraints provided by them

Finding	Constraint
LTD can be induced at the spinous region of MSNs of NAc[17,18,28]	Energy applied at the spinous region leads to depression of potentials at the recording electrode placed at the postsynaptic region or on MSN soma
LTD induction has a time delay following stimulation[17,18] comparable to that of LTP induction[13,14]	A time-dependent cellular change is taking place during the delay period following LTD stimulation
Similar to LTP, LTD is also NMDA receptor-dependent[82]	LTD induction takes place through activation of NMDA receptors of glutamatergic synapses
When rewards or conditioned stimuli that predict reward are presented, dopamine neurons in the VTA increase their firing[91,92] releasing dopamine in their terminals that synapse with spines of MSNs in NAc	Dopamine produces certain changes at the spines of MSNs that synapse with excitatory inputs
Drugs of abuse such as cocaine increase dopamine levels in the NAc[28]	Dopamine has certain actions on the spines of MSNs that synapse with excitatory inputs
Dopamine attenuates postsynaptic potentials elicited by stimulation of different excitatory inputs to NAc shell region[40]	Action of dopamine on spines of MSNs that synapse with excitatory inputs attenuates postsynaptic potentials when these excitatory inputs are stimulated through a mechanism
Dopamine reduces excitability of MSNs *in vitro*[93]	Action of dopamine on the spines of MSNs that synapse with excitatory inputs results in inhibition of MSNs through a mechanism
Exposure to cocaine leads to attenuation of postsynaptic potentials[42]	Action of cocaine leads to release of dopamine that acts on spines of MSNs that synapse with excitatory inputs and results in attenuation of postsynaptic potentials
In response to natural rewards and cocaine exposure, a major set of MSNs show depression of firing rate[43-46]	Rewards and drugs cause release of dopamine from VTA and dopamine's action on spines of MSNs that synapse with excitatory inputs result in reduced firing rate of MSNs through a mechanism
Synchronization of membrane potential states in a population of NAc neurons [53]	A mechanism through gap junctions between inhibitory neurons in VTA that provides inputs to NAc neurons and/or a mechanism at the level of spines of MSNs
Brain functions occur optimally in a narrow range of frequency of oscillating extracellular potentials especially that of background alpha rhythm as evident from electroencephalogram (EEG) findings[49]	Regional oscillations of extracellular potentials are expected to be related to oscillating extracellular potentials of the system
Summary of findings	**Inter-connected constraints**
Drugs cause release of dopamine from VTA, which in turn cause attenuation of postsynaptic potentials and depression of MSNs in NAc. Application of energy is able to induce delayed LTD through scaled up changes expected to occur normally at the synaptic region of NAc, which is likely responsible for generating internal sensation of pleasure	Dopamine does certain unique changes at the spines of MSNs of NAc that synapse with excitatory inputs to cause attenuation of postsynaptic potentials, depression of MSNs and promotes experimental induction of LTD. This inter-connected operation is expected to explain a mechanism that generates inner sensation of pleasure

Constraints provided by disparate findings can be used to find inter-connectable explanations for deriving a unique mechanism, which is expected to provide an explanation for the generation of internal sensation of pleasure. NAc: Nucleus accumbens; LTD: Long-term depression; MSNs: Medium spiny neurons; NMDA: N-methyl-D-aspartate; VTA: Ventral tegmental area.

MECHANISM OF PLEASURE AND INTERCONNECTED EXPLANATIONS FOR FINDINGS IN NAc

By keeping (1) the correlation between associative learning and LTP induction[11]; and (2) the ability of inter-LINKed spines of excitatory synapses to induce internal sensation of memory[3] as reference mechanisms, a reasonable expectation is that a mechanism for generating internal sensation of pleasure that satisfies constraints from different findings in NAc (Table 1) will become possible. Dendritic arbors of different MSNs overlap. Energy is applied to induce LTD at the synaptic locations of MSNs of NAc where spines present on different dendrites are abutted. One set of these spines receive inputs from excitatory neurons of different brain regions and another set of spines receive inputs from inhibitory neurons of VTA. In addition, the heads or necks of spines that synapse with excitatory inputs receive dopaminergic inputs[31] (Figure 3). Spines of excitatory synapses that also receive dopaminergic inputs enlarge by the action of dopamine[16]. Furthermore, a scaled-up electrophysiological change responsible for the generation of pleasure is expected to take place during experimental LTD induction at these synaptic locations.

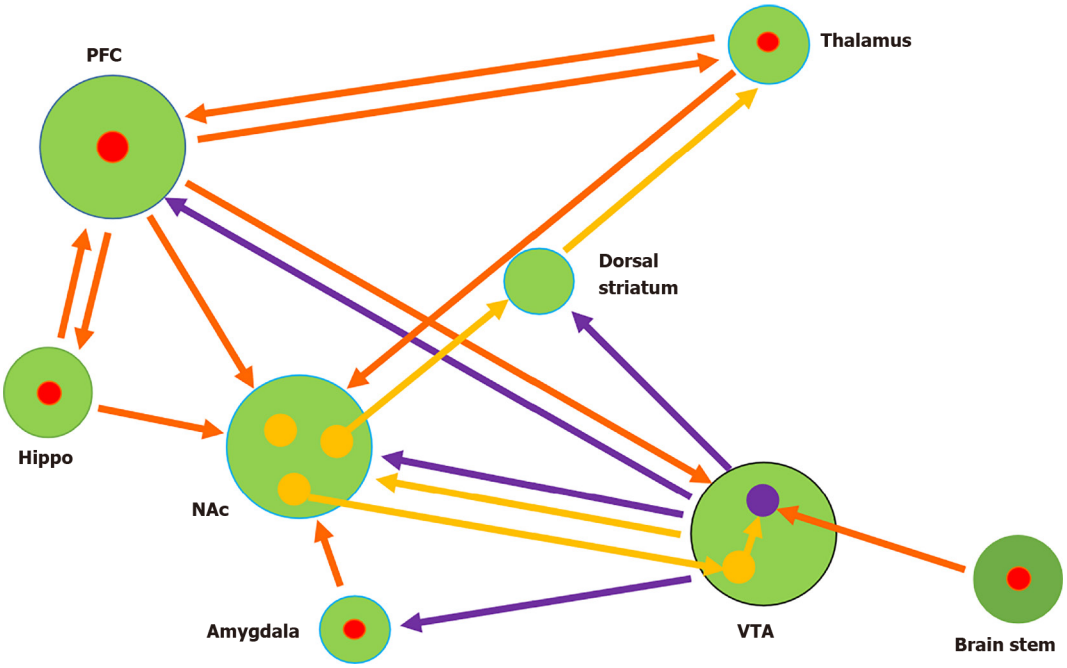


Figure 2 Input and output connections of nucleus accumbens. One set of spines of medium spiny neurons (MSNs) in the nucleus accumbens receive excitatory inputs (red arrows) from several regions. The same spines of MSNs that receive excitatory inputs receive dopaminergic inputs (violet arrows) from ventral tegmental area (VTA). Another set of MSN spines receive inputs from inhibitory interneurons (orange arrow) in the VTA. Large green circles: Different brain regions. Small circles: Predominant cell types within brain regions (Red: Excitatory; Orange: Inhibitory; Violet: Dopaminergic). PFC: Prefrontal cortex; NAc: Nucleus accumbens; VTA: Ventral tegmental area.

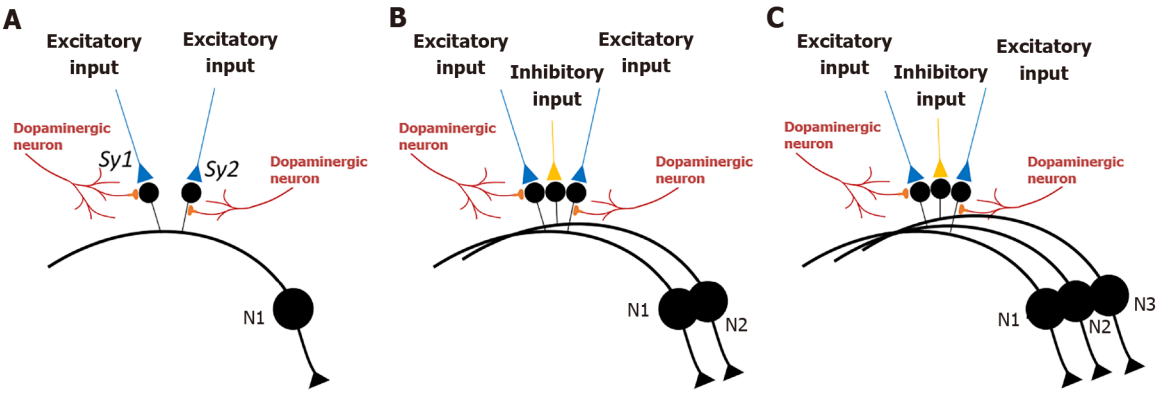


Figure 3 Interactions between spines of medium spiny neurons that synapse with excitatory inputs and spines of medium spiny neurons that synapse with inhibitory inputs. A: Adjacent spines (small black circles) on the dendrite of a medium spiny neuron (MSN) (N1) (cell body is drawn in a large black circle) that synapse with two excitatory inputs (in blue) to form synapses Sy1 and Sy2). Golgi staining shows that spines are physically well separated from each other on the dendrites of MSNs[23,24] such that the inter-spine space is occupied by spines of other dendrites or processes of other neurons or glial cells. This increases the probability that the nearest spine to a spine on the dendrite of a MSN is most likely a spine that belongs to another neuron, or in rare cases belongs to another branch of the same neuron. Note that dopaminergic inputs synapse either onto the head or neck region of spines that synapse with excitatory inputs; B: In between two adjacent spines of MSN N1 shown in figure A, there is a spine that belongs to a second MSN (N2). This spine synapses with an inhibitory input (in orange). All the spines are electrically insulated from each other by fluid extracellular matrix. Natural stimulants or cocaine abuse causes release of dopamine that will cause enlargement of spines that synapse with excitatory inputs. Since the spine that synapses with the inhibitory input is spatially interposed between the expanding spines, inter-postsynaptic functional LINKs are formed between those three spines; C: Same configuration of two spines of MSNs that synapse with excitatory inputs and one middle spine synapsing with inhibitory input. Here, these spines belong to three different MSNs.

There are two main methods by which LTD can be induced. (1) Low-frequency stimulation induces LTD that requires activation of N-methyl-D-aspartate receptors (NMDARs)[33,34]. Modest activation of NMDARs that can be used to induce LTD[28] may involve AMPAR endocytosis[35]; (2) By keeping postsynaptic depolarization below a threshold, a tetanic stimulation that normally induces LTP can induce LTD [36]. Removal of surface AMPARs occurs during induction of both NMDAR-dependent LTD[37,38], and metabotropic glutamate receptor-LTD[39,40]. Since endocytosis of vesicles containing AMPAR subunits during expression of LTD in NAc

[18] is associated with usage of membrane segments from lateral spine head regions that reduces spine size, it can lead to reversal of large number of existing IPLs. Even though reversal of existing IPLs can explain LTD similar to that of LTP decay[13], it is necessary to explain LTD as an active mechanism that requires energy for its experimental induction. Based on findings in NAc (Table 1), it is also necessary to explain (1) Attenuation of postsynaptic potentials by the effect of dopamine on MSN spines that synapses with excitatory inputs[41,42]; and (2) Reduced firing rate of MSNs[43-46], in addition to finding a matching explanation for the generation of internal sensation of pleasure. This has been remaining a challenge.

In the above contexts, main question is whether it is possible to explain internal sensation of pleasure and all the findings in Table 1 in terms of IPL mechanism. It is known that drugs of abuse such as cocaine lead to increased dopamine levels in the NAc[28]. Dopamine is known to cause spine enlargement[16]. Since dopaminergic inputs synapse with spines that receive excitatory glutamatergic inputs, this is expected to cause enlargement of those spines of MSNs. This forces these spines to form IPLs with all their abutted spines. Since some MSN spines synapse with excitatory inputs and others with inhibitory inputs, it is necessary to take into account the possibility for IPL formation between these spines (Figure 3B). In this context, IPL formation between MSN spines that synapse with inhibitory inputs and MSN spines that synapse with excitatory inputs can be examined in the light of the previous view that inhibitory inputs at the input level have a role in information processing[47]. It is necessary to combine all this information to obtain a solution for the challenge described in the previous paragraph.

Since LTP induction in the cortex usually requires low doses of gamma-amino butyric acid$_A$ ($GABA_A$) receptor antagonist bicuculline[48] for concomitant reduction of GABAergic inhibition, it shows the necessity to block activation of spines that synapse with inhibitory inputs. When spines that receive inhibitory inputs are in large numbers, such as in NAc, a mere reduction in GABAergic inhibition alone will not be able to induce LTP. This is because the numbers of spines that receive excitatory inputs are comparatively less to form IPLs between them alone to induce LTP. Now the question is, "What is the effect of application of energy on the MSN spines that receive excitatory inputs and MSN spines that receive inhibitory inputs that are distributed somewhat equally?" This increases the probability for the formation of IPLs between those spines. This can lead to propagation of hyperpolarization from the spines that synapse with inhibitory inputs to neutralize and even hyperpolarize the spines that synapse with excitatory inputs. In experimental LTD stimulation, this will result in depression of net potentials at the recording electrode responsible for LTD.

Now the question is, "Can formation of IPLs between MSN spines that synapse with excitatory inputs and MSN spines that synapse with inhibitory inputs explain the generation of internal sensation of pleasure?" At this juncture, a reasonable inference is that semblance generated at the location where LTD can be experimentally induced is associated with internal sensation of pleasure. Now, one can ask, "What type of a semblance can be anticipated based on the nature of inputs at the spines of MSNs and IPLs that are formed between them?" In physiological conditions, hyperpolarization of spines that receive inhibitory inputs is expected to propagate to spines that receive excitatory inputs through the IPLs formed between them. This is expected to generate a conformational change in the net local semblance induced from all the inter-LINKed spines of MSNs and contribute to internal sensation of pleasure (Figure 4). Brain functions such as pleasure take place only in a state of normal consciousness associated with a narrow range of oscillating extracellular potentials as evident from EEG findings[49]. Synaptic transmission at the synapses and propagation of potentials across the IPLs are expected to contribute vector components to both regional and system level oscillating extracellular potentials[3]. Narrow range of background oscillating extracellular potentials is expected to be generated from continuous reactivation of the large number of IPLs formed from common background stimuli to which nervous system is exposed[50,51]. The latter event continues to generate a background semblance in which internal sensation of pleasure is formed (Figure 4). Explanation for the functional significance of background semblance was explained previously[9].

Several inhibitory neurons in the VTA are expected to get activated through gap junctions between them similar to that contribute to cortical oscillations[52]. It can lead to synchronization of membrane potential states in a population of NAc neurons[53] and can explain how continuous reactivation of newly formed IPLs in NAc maintains pleasure. In physiological conditions, formation of IPLs between MSN spines that synapse with excitatory inputs and MSN spines that synapse with inhibitory inputs can explain how it leads to attenuation of postsynaptic potentials while getting

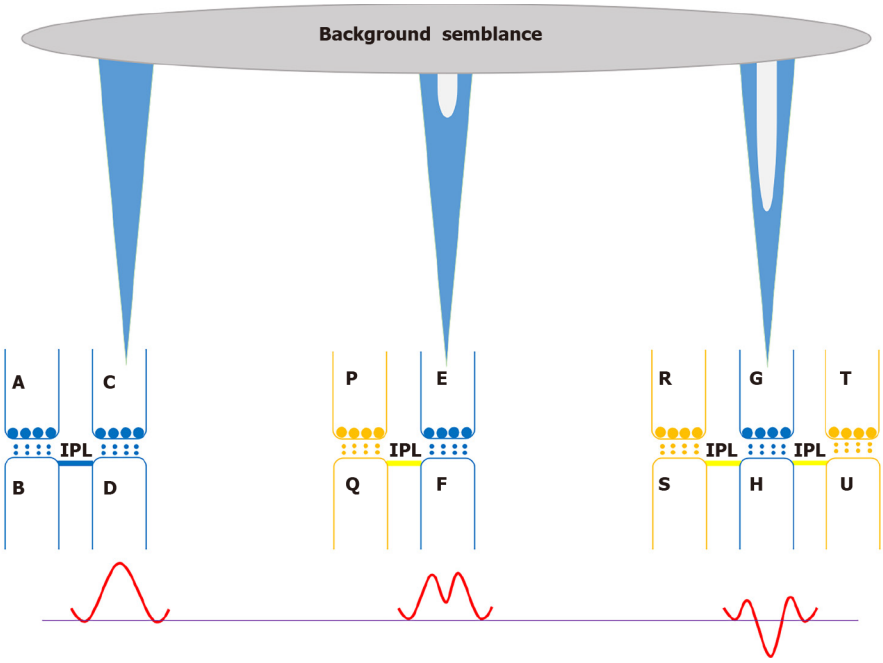


Figure 4 A schematic representation of units of internal sensations whose integral generates pleasure in a background net semblance of the system. Left: Normal semblance as shown in Figure 1. Inter-postsynaptic functional LINK (IPL) between spines B and D that receive excitatory inputs (in blue). An action potential arriving at presynaptic terminal A from a stimulus depolarizes its postsynaptic terminal B, which in turn propagates through the IPL B-D and depolarizes (shown as a positive waveform) inter-LINKed spine D. This generates units of internal sensations (shown as a blue triangle projected upwards from presynaptic terminal C that denotes semblance). Middle: Reactivation of an IPL between spine Q of a medium spiny neuron (MSN) that synapse with an inhibitory input (in orange) and another spine F of a MSN that synapse with an excitatory input (in blue) results in spread of hyperpolarization from spine Q to spine F. This leads to changes in both the waveform of spine depolarization (red waveform) and conformation of semblance (shown as a dip in the blue triangle). Right: Here, spine H that synapses with an excitatory input (in blue) forms IPLs with spines S and U that synapse with inhibitory inputs (orange). Net effect of hyperpolarization results in profound changes in both waveform of spine depolarization (red waveform) and conformation of semblance (shown as a deep dip in the blue triangle). Net effect of changes in semblances from all the inter-LINKed spines of MSNs in nucleus accumbens (NAc) is expected to generate a special semblance of pleasure.

exposed to dopamine[41]. In addition, it can also explain reduced firing of MSNs when animals are exposed to both natural rewards and cocaine[43-46]. The scaled-up change in experimental stimulation that generates LTD is a net effect of depression in the sum of potentials arriving at the recording electrode. A summary of these interconnected findings is shown in Figure 5.

HOMEOSTATIC CHANGES DURING DRUG ABUSE AND WITHDRAWAL

IPL formation involves interaction between outer membranes of spines by excluding the insulating fluid ECM[3]. Exocytosis of intra-cytoplasmic vesicles provides membrane segments that allow re-organization of the cell membrane at the lateral margins of spines that can promote IPL formation. Conversely, endocytosis of GluR1 AMPAR vesicles is associated with a reversal of LTP (LTP decay)[13]. Similar mechanisms can be expected to cause the formation and reversal of IPLs during LTD induction and decay respectively.

After 10 to 14 d of repeated *in vivo* cocaine exposure, both the ratio of AMPAR/NMDAR-mediated excitatory postsynaptic currents (EPSCs) and magnitude of LTD are reduced[17]. One of the reasons for a reduction in the AMPAR/NMDAR - mediated EPSC ratio is a decrease in the number of AMPARs. Based on the IPL mechanism, cocaine exposure results in the enlargement of spines that predisposes the IPLs formed between these spines to undergo fusion pore formation. In this context, endocytosis of vesicles containing GluR1AMPARs following cocaine administration can be viewed as a homeostatic mechanism for preventing IPL fusion. During vesicle endocytosis, usage of membrane segments from lateral spine head regions can reduce the size of spine heads and reverse extreme changes of IPLs such as IPL fusion. Endocytosis of these vesicles observed during experimental LTD induction[18,54,55] can be viewed as a scaled-up physiological response for preventing IPL fusion, especially in locations where dopamine is released. In this context, the finding that a challenge dose of cocaine after weeks of cocaine withdrawal terminates withdrawal

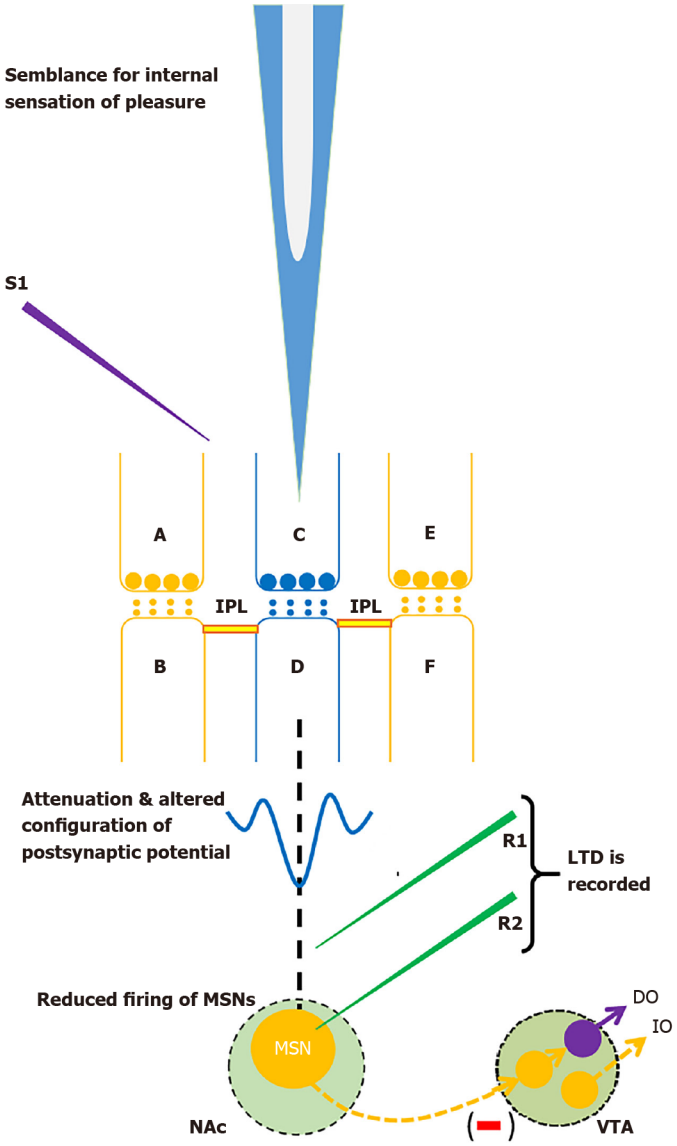


Figure 5 Nucleus accumbens circuitry that matches with constraints from several findings. Spines B and F belonging to different medium spiny neurons (MSNs) synapse with inhibitory inputs arriving through presynaptic terminals A and E respectively. Spine D on a third MSN synapses with excitatory input arriving through presynaptic terminal C. Two inter-postsynaptic functional LINKs (IPLs) are formed between spines B, D and F. These IPLs between spines that synapse with excitatory and inhibitory inputs lead to mixing of depolarization on the spines that synapse with excitatory input and hyperpolarization on the spines that synapse with inhibitory inputs. This leads to alternation of configuration of the net postsynaptic potentials as shown in a trace. Net semblance from a large number of inter-LINKed spines is expected to generate a special semblance for internal sensation of pleasure. Due to propagation of hyperpolarization, sum of potentials reaching many MSNs may not cross the threshold for firing, which leads to reduced firing of MSNs. A specific stimulation pattern applied at the presynaptic region using stimulating electrode S1 results in the formation of a large number of the above-mentioned types of IPLs in a time-dependent manner (inferred from delay between stimulation and long-term depression (LTD) induction[17,18]) resulting in LTD recorded from either recording electrode R1 (extracellular field recording) or R2 (whole-cell recording). Two inhibitory inputs to MSN and one inhibitory output from MSN are shown in orange. Excitatory synapse is shown in blue. Dopaminergic neuron of ventral tegmental area is shown in violet. DO: Dopaminergic output; IO: Inhibitory output; VTA: Ventral tegmental area.

along with endocytosis of AMPARs[28] can be considered as an augmented homeostatic mechanism.

During early withdrawal, administration of dopamine alone restores both spine structure and LTD[56] that can be explained in terms of IPL formation between MSN spines that synapse with excitatory inputs and MSN spines that synapse with inhibitory inputs indicating that the system is highly dynamic. During later periods of withdrawal, an increase in AMPARs at the membrane surface is observed[57,58]. During this time, a strong potentiation of AMPAR-mediated synaptic transmission is observed in the synapses on the spines of NAc MSNs. At this time, a single exposure to cocaine suddenly reverses the synaptic potentiation to depression[59]. This indicates that after a very lengthy drug-free period, the system reaches a near normal state and starts responding like a naïve system by forming IPLs between spines that synapse with excitatory inputs and spines that synapse with inhibitory inputs.

PATHOLOGICAL CHANGES FOLLOWING DRUG ABUSE

Inter-spine fusion is a possible consequence of drug abuse

Based on the IPL mechanism, conditions such as excessive drug use that cause excessive release of dopamine can lead to progression of IPLs to an extreme end of the spectrum of IPL changes, namely IPL fusion[6]. Defects in normal homeostatic mechanisms described in the above paragraph or changes in membrane composition can augment IPL fusion. Fusion between expanding spines matches with the previous observation of dye diffusion between neurons in NAc under the influence of dopamine[60]. Since transcriptomes of even neighboring neurons of similar type are different in the brain[61-63], IPL fusion that occurs between spines that belong to two neurons (Figure 3B and C) can lead to cytoplasmic content mixing and protein precipitation. An initial cellular response is expected to seal off the IPL fusion pore. When this fails, neurons are expected to protect themselves by removing fused spines from them[64], which can explain spine loss during cocaine abuse[65,66]. Loss of spines at the input regions of NAc MSNs in cocaine users will reduce the number of abutted spines and will reduce the probability of IPL formation. This will prevent experimental induction of LTD as evidenced from different studies[67,68].

Drug addiction

Major consequence of IPL fusion is the eventual loss of spines of MSNs[65,66] as a homeostatic mechanism to protect neuronal cells[64]. Since "non-addicted" animals regain the ability to generate LTD after two weeks of discontinuing self-administration of cocaine[68], it indicates that these animals may not have lost their spines. However during early stages of spine loss, the remaining spines can form IPLs to generate internal sensation of pleasure only if they can expand. This necessitates release of dopamine that in turn necessitates the availability of drugs. A natural consequence of this is initiation of drug seeking behavioural motor actions elicited through separate pathways. In later stages when more spines are lost, more amount of drug will become necessary even to maintain internal sensation of normal comfort. At this stage, reduced number of spines on MSNs will lead to persistent impaired LTD in "addicted" animals[68].

DISCUSSION

LTD can be experimentally induced in many brain regions and by different methods. Translating this to understand how it is related to conformational changes in semblance and the nature of internal sensations require examination of all the connections and findings at those regions. Excitatory neurons are controlled by inhibitory neurons both at the output level, for example, in the visual cortex[69] and at the input level[70,71]. The present work has explained a new testable function of inhibitory neurons at their output level. By explaining IPL formation between MSN spines that synapse with inhibitory inputs and MSN spines that synapse with excitatory inputs, it became possible to provide mechanistic explanations for previous assumptions that (1) Increased firing of VTA dopaminergic neurons encode an array of sensory, motor and cognitive variables[72]; and (2) Reduced activity of NAc MSNs encode reward[73-76]. The finding that coupling of potentials between MSNs were found to occur only in neurons that also showed dye coupling[60] matches with the IPL mechanism explained in the present work because IPLs with fusion pores can allow both dye diffusion through the fusion pore and propagation of potentials across the connecting membrane segments. The inference that input-specific filtering of excitatory inputs in the NAc is provided by dopamine[77] can be explained in terms of IPL formation between MSN spines that both synapse with excitatory inputs and enlarge under the influence of dopamine and MSN spines that receive inhibitory inputs.

Further examination is needed to understand the role of cholinergic inputs that synapse with the spines of MSNs in NAc[78]. It is also necessary to examine the difference in dopamine's actions on MSN spines in the shell and core regions of NAc [79,80] for their contributions on pleasure generation. Comparable findings in neurons of lateral hebenula, a brain region associated with reward, whose spines synapse with excitatory, inhibitory and dopaminergic inputs[81]can be examined to further understand this related brain function.

Fast kinetics of AMPA current in glutamatergic synapses allows initial depolarization of the spine head region. It is known that glutamate released from the presynaptic boutons is necessary to depolarize their spines, which will relieve blockage of NMDARs by Mg^{2+}[82]. Furthermore, postsynaptic depolarization below certain threshold induces LTD when tetanic stimulation that normally induces LTP is used[36]. Hyperpolarization from inter-LINKed spines that synapse with inhibitory inputs can provide suitable conditions for the above. It is also possible that timing of hyperpolarization propagating from an inter-LINKed spine that synapse with an inhibitory input also determines the conformation of semblance generated at the spines of excitatory synapses shown in Figures 4 and 5. Understanding details of the mechanism can provide information regarding selection of different types of glutamate receptors, their distribution and functional roles in different brain regions.

Based on the present work, sequence of appearance of neurotransmitters glutamate and GABA[83,84] is likely to provide information about the period when internal sensation of pleasure started appearing during evolution. The enzyme glutamic acid decarboxylase (GAD) catalyzes decarboxylation of glutamate to form GABA. Even though GABAergic interneurons were present in the common ancestor of all amniotes [85], it is difficult to trace the sequence of appearance of glutamatergic and GABAergic neurons. A possibility is that as neurons started receiving a large number of inputs, several combinations of IPLs started generating different internal sensations, which allowed natural selection of neurons that started expressing GAD. By selecting configurations of inputs that led to the formation of IPLs generating internal sensation of pleasure, animals were likely able to seek certain items and perform certain actions that were essential for survival, which those animals would not have performed otherwise.

CONCLUSION

By viewing pleasure as a first-person internal sensation, it was possible to extend IPL mechanism to formulate a framework of a specific mechanism taking place at the dendritic spine regions of MSNs in NAc responsible for pleasure. It matches with constraints provided by disparate findings such as the ability to induce robust LTD in NAc from naïve animals, impaired ability to induce LTD in addicted state, attenuation of postsynaptic potentials by cocaine, and reduced firing of MSNs in response to cocaine or dopamine. IPL mechanism that provided inter-connectable explanations for pleasure and disparate findings in NAc can be subjected to further verification. Since IPLs are expected to be of roughly $10nm^2$ in area as inferred from theoretical studies of membrane bilayers[86], advanced microscopic methods are necessary to detect their real-time formation, stabilization, and reversal in normal conditions and conversion to fusion states in addicted animals.

ACKNOWLEDGEMENTS

I acknowledge the support from Neurosearch Center, Toronto.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 696-710

DOI: 10.5498/wjp.v11.i10.696

ISSN 2220-3206 (online)

REVIEW

Metabolic disturbances associated with antipsychotic drug treatment in patients with schizophrenia: State-of-the-art and future perspectives

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Author contributions: Chang SC and Goh KK contributed equally to this work; Chang SC, Goh KK, and Lu ML performed the literature search and reviewed the selected manuscripts; Chang SC wrote the first draft; Goh KK and Lu ML contributed to the final version of the manuscript; All authors have read and approve the final manuscript.

Supported by the Higher Education Sprout Project of the Ministry of Education, No. DP2-109-21121-01-N-07-04; and the Ministry of Science and Technology, No. MOST109-2314-B-038-083.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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Abstract

Metabolic disturbances and obesity are major cardiovascular risk factors in patients with schizophrenia, resulting in a higher mortality rate and shorter life expectancy compared with those in the general population. Although schizophrenia and metabolic disturbances may share certain genetic or pathobiological risks, antipsychotics, particularly those of second generation, may further increase the risk of weight gain and metabolic disturbances in patients with schizophrenia. This review included articles on weight gain and metabolic disturbances related to antipsychotics and their mechanisms, monitoring guidelines, and interventions. Nearly all antipsychotics are associated with weight gain, but the degree of the weight gain varies considerably. Although certain neurotransmitter receptor-binding affinities and hormones are correlated with weight gain and specific metabolic abnormalities, the precise mechanisms underlying antipsychotic-induced weight gain and metabolic disturbances remain unclear. Emerging evidence indicates the role of genetic polymorphisms associated with antipsychotic-induced weight gain and antipsychotic-induced metabolic disturbances. Although many guidelines for screening and monitoring antipsychotic-induced metabolic disturbances have been developed, they are not routinely implemented in clinical care. Numerous studies have also investigated strategies for managing antipsychotic-induced metabolic disturbances. Thus, patients and their caregivers must be educated and motivated to pursue a healthier life through smoking cessation and dietary and physical activity programs. If lifestyle intervention fails, switching to another antipsychotic drug with a lower metabolic risk or adding adjunctive medication to mitigate weight gain should be considered. Antipsychotic medications are essential for schizophrenia treatment, hence clinicians should monitor and manage the resulting weight gain and metabolic

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Taiwan

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 30, 2021
Peer-review started: January 30, 2021
First decision: March 8, 2021
Revised: March 16, 2021
Accepted: August 31, 2021
Article in press: August 31, 2021
Published online: October 19, 2021

P-Reviewer: Kotzalidis GD
S-Editor: Liu M
L-Editor: Filipodia
P-Editor: Yu HG

disturbances.

Key Words: Antipsychotics; Metabolic disturbances; Weight gain; Schizophrenia; Monitor; Intervention

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Core Tip: Metabolic disturbances associated with antipsychotic drug treatment are prevalent in patients with schizophrenia. We herein discuss the epidemiology, the underlying mechanisms, monitoring, and intervention strategies of antipsychotics related metabolic disturbances.

Citation: Chang SC, Goh KK, Lu ML. Metabolic disturbances associated with antipsychotic drug treatment in patients with schizophrenia: State-of-the-art and future perspectives. *World J Psychiatr* 2021; 11(10): 696-710
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/696.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.696

INTRODUCTION

Patients with schizophrenia have a two to three times higher mortality rate[1,2] and a 20%–25% shorter life expectancy[3] compared with the general population. In addition to the considerably increased risks of suicide, cancer, and respiratory diseases, cardiovascular mortality is a leading cause of excess mortality in patients with schizophrenia[4,5]. Metabolic syndrome and obesity are major cardiovascular risk factors in patients with schizophrenia[5,6].

Before the introduction of the first antipsychotic drug chlorpromazine in 1952, cohort studies noted an increased incidence of abnormal glucose metabolism in patients with schizophrenia[7]. Studies also found that increased fasting and postprandial blood glucose levels in drug-naïve patients with schizophrenia were partly correlated with the severity of their illness[7,8]. Although such metabolic disturbances are partially attributed to unhealthy lifestyle behaviors such as smoking, poor diet, and physical inactivity[9], evidence also indicates a shared pathophysiology between schizophrenia and metabolic disturbances[10]. Meta-analyses of first-episode and drug-naïve patients with schizophrenia have indicated impaired glucose homeostasis and subclinical dyslipidemia before antipsychotic treatment[8,11]. Impaired glucose tolerance in the first-degree relatives of patients with schizophrenia further supports the role of genetic predisposition between schizophrenia and metabolic disturbances[12]. Researchers aim to determine the common susceptible genes that contribute to both schizophrenia and type 2 diabetes mellitus[13-15]. Other pathobiological factors contributing to metabolic disturbances in patients with schizophrenia have also been proposed. Mück-Seler *et al*[16] found that patients with schizophrenia have hypothalamic–pituitary–adrenal axis dysregulation and increased plasma cortisol levels, and evidence shows that hypothalamic–pituitary–adrenal axis dysregulation may play a significant role in the development of metabolic syndrome [17]. Researchers have also suggested that schizophrenia and metabolic syndrome are both related to inflammatory and immune mechanisms[18,19].

Additionally, antipsychotic treatment may exacerbate the metabolic disturbances in patients with schizophrenia. Antipsychotic drugs are the drugs of choice for treating patients with schizophrenia, and certain drugs are also indicated to treat a wide range of mental illnesses, including bipolar disorder, treatment-resistant depression, Tourette syndrome, and aggressive behavior in autism. These drugs are categorized as first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). FGAs act on the dopaminergic system by blocking the dopamine type 2 (D2) receptors. Compared with FGAs, SGAs treat the negative, cognitive, and mood symptoms of schizophrenia more effectively and result in fewer extrapyramidal symptoms at clinically effective doses[20]. Therefore, SGAs may result in greater treatment adherence and psychotic relapse prevention.

Although a meta-analysis indicated that nearly all antipsychotics are associated with weight gain after prolonged exposure[21], certain SGAs are associated with a greater liability of weight gain and metabolic disturbances than high-potency FGAs are[22]. However, studies have shown that antipsychotic use is associated with a decreased risk of all-cause, cardiovascular, and suicide mortality[23,24]. Such findings on long-term mortality outcomes may appear inconsistent with the metabolic side effects of antipsychotic use. This disconnection is likely to due to the improvement of psychopathology associated with antipsychotic treatment, which subsequently may result in healthy lifestyle behaviors and use of health care services for physical illnesses[23,25].

Although antipsychotic medications are essential for treating schizophrenia, clinicians should compare the risks and benefits in choosing the most favorable treatment. This review focused on the adverse effects of weight gain and metabolic disturbances induced by antipsychotic drugs.

ANTIPSYCHOTIC DRUGS AND WEIGHT GAIN

Studies have shown the prevalence of obesity [body mass index (BMI) over 30 kg/m^2] among people with schizophrenia is 42%–60%[26,27]. Several[28,29] but not all[30,31] studies have reported that antipsychotic-naïve patients with schizophrenia are at a higher risk of overweight and obesity. Additionally, weight gain is a well-known side effect of antipsychotic drugs in patients with schizophrenia, influencing 15%–72% of patients[28]. Among FGAs, low-potency ones such as chlorpromazine and thioridazine are related to a greater risk of weight gain than high-potency ones such as haloperidol and fluphenazine[32].

Various SGAs are also associated with varying probabilities of weight gain: Clozapine and olanzapine carry the highest risk; quetiapine, risperidone, and paliperidone an intermediate risk; and aripiprazole, ziprasidone, and lurasidone the lowest risk[20,33,34]. The difference between long-acting injectable and oral SGAs relative to the incidence of weight gain is not significant[35]. Notably, the greatest degree of weight gain in drug-naïve patients with schizophrenia occurs in the first few months after antipsychotic commencement[36]. Although the rate of weight gain then gradually decreases, patients might continue to gain weight for 1–4 years[37]. An early weight gain of > 5% in the first month is the best predictor of long-term weight gain [38].

ANTIPSYCHOTIC DRUGS AND METABOLIC DISTURBANCES

Several attempts have been made by various organizations to establish diagnostic criteria for metabolic syndrome[39]. The World Health Organization proposed the first definition of metabolic syndrome in 1998[40]. In 2001, the National Cholesterol Education Program Adult Treatment Panel III updated the guidelines for metabolic syndrome[41]. The limitation of the aforementioned definitions is that because cutoff values of obesity specific to certain populations are not defined, such cutoff values are not applicable to different ethnic groups. In 2004, Tan *et al*[42] proposed a modified National Cholesterol Education Program Adult Treatment Panel III criteria for metabolic syndrome in Asian populations. In 2006, the International Diabetes Federation provided a worldwide definition of metabolic syndrome with ethnicity-specific criteria for central obesity[43]. Table 1 illustrates the different definitions of metabolic syndrome from different organizations.

Metabolic syndrome is a group of health problems that includes central obesity, hyperglycemia, dyslipidemia, and hypertension, with central obesity being the primary feature[44]. Central obesity is associated with insulin resistance, which finally results in type 2 diabetes mellitus and cardiovascular diseases. Metabolic syndrome is highly prevalent in patients with schizophrenia; the overall prevalence rate being 32.5%[45]. Results from the Clinical Antipsychotic Trials of Intervention Effectiveness schizophrenia trial and comparison with national estimates from the Third National Health and Nutrition Examination Survey revealed that men and women from the Clinical Antipsychotic Trials of Intervention Effectiveness trial were 138% and 251% more likely, respectively, to have metabolic syndrome than patients from the Third National Health and Nutrition Examination Survey matched sample[46].

Table 1 Diagnostic criteria for metabolic syndrome

Organization, Year	WHO, 1988	NCEP/ATP III, 2001	Modified NCEP/ATP III for Asians, 2004	IDF, 2006
Criteria	Glucose intolerance, IGT, diabetes mellitus, or insulin resistance together with two or more of the following:	Three or more of thefollowing:	Three or more of thefollowing:	Central obesity as defined by ethnicity/race, specific WC, but can be assumed if BMI > 30 kg/m^2 and with two or more of the following:
	BP: ≥ 140/90 mmHg	FPG: ≥ 110 mg/dL[1] or on treatment for DM	FPG: ≥ 110 mg/dL[1] or on treatment for DM	FPG: ≥ 100 mg/dL or on treatment for DM
	Abdominal obesity: WHR > 0.9 and > 0.85 for men and women, respectively, and/orBMI: > 30 kg/m^2	BP: ≥ 130/85 mmHg	BP: ≥ 130/85 mmHg	BP: ≥ 130/85 mmHg or on treatment
	Triglycerides: ≥ 150 mg/dL or onTreatment	Triglycerides: ≥ 150 mg/dL or on treatment	Triglycerides: ≥ 150 mg/dL or on treatment	Triglycerides: ≥ 150 mg/dL or on treatment
	HDL-C: < 35 mg/dL for men and < 39 mg/dL for women	HDL-C: < 40 mg/dL for men and < 50 mg/dL for women	HDL-C: < 40 mg/dL for men and < 50 mg/dL for women	HDL-C: < 40 mg/dL for men and < 50 mg/dL for women or on treatment
	Urine albumin excretion rate: ≥ 2 0 μg/min or urine albumin to creatinine ratio: ≥3 0 mg/g	WC: ≥ 102 cm for men and ≥ 88 cm for women	WC: ≥ 90 cm for men and ≥ 80 cm for women	

[1]FPG ≥ 100 mg/dL modified in 2004 according to the International Diabetes Federation definition of impaired fasting glucose. The 2001 definition of National Cholesterol Education Program Adult Treatment Panel III identified fasting plasma glucose ≥ 110 mg/dL as elevated. BMI: Body mass index; FPG: Fasting plasma glucose; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; IR: Insulin resistance; IDF: International Diabetes Federation, NCEP/ATP III: National Cholesterol Education Program Adult Treatment Panel III; WC: Waist circumference; WHR: Waist-to-hip ratio; WHO: World Health Organization.

As mentioned, individual antipsychotic drugs have significant differences in their effects on metabolic disturbances in correlation with their weight gain probabilities [22]. However, some case reports have suggested that substantial weight gain or obesity may not be a factor in up to 25% of cases of new-onset diabetes during antipsychotic treatment[47]. Other studies have reported that olanzapine exerts metabolic changes within days in healthy volunteers without a significant change in body weight[48,49]. Evidence suggests that antipsychotics may directly influence pancreatic beta cells, resulting in time-dependent changes in insulin secretion with initial hypoinsulinemia and subsequent compensatory hyperinsulinemia[50].

MECHANISM UNDERLYING WEIGHT GAIN AND METABOLIC DISTURBANCES DUE TO ANTIPSYCHOTIC DRUGS

Several neurotransmitters and hormones thought to be involved in the management of satiety, feeding, and glucose metabolism have been implicated in the mechanism of antipsychotic-induced weight gain (AIWG) and metabolic disturbances.

Hormones

Various peptide hormones, including leptin, adiponectin, ghrelin, orexin, and cholecystokinin (CCK), play critical roles in the regulation of energy homeostasis and are suggested to be biomarkers of metabolic disturbances. Studies have indicated that serum leptin level increases during antipsychotic treatment[51,52]. Although leptin acts to inhibit food intake, studies have suggested that antipsychotics could induce or exacerbate a leptin-resistance status, which may contribute to aggravated obesity[52]. However, other findings support the possibility of another mechanism involving antipsychotic-induced epigenetic changes to leptin or leptin receptor genes[53].

Adiponectin can also reduce food intake, and a meta-analysis by Bartoli *et al*[54] indicated that treatment with clozapine and olanzapine is associated with decreased adiponectin levels. Decreased adiponectin levels may result in insulin resistance and increased risk of inflammation independent of adiposity[55]. A study revealed that some SGAs, especially clozapine and olanzapine, might exhibit a time-dependent effect on adiponectin levels[56]. Initially, the up-regulation of adiponectin might compensate for the deleterious effect of olanzapine and clozapine on glucose

homeostasis. Then, a new energy balance equilibrium is regained during a short-term treatment, resulting in the return of blood adiponectin levels to the baseline. Finally, the failure of adiponectin up-regulation pushes blood adiponectin levels further below the baseline after long-term treatment.

Ghrelin, however, is a hunger-inducing hormone. Reports on the association between antipsychotic treatment and ghrelin level changes are inconsistent, although three long-term studies reported increased ghrelin levels in patients on SGAs with weight gain liabilities[51]. Acylated ghrelin and desacylated ghrelin are the two main forms of ghrelin and play opposing roles in energy homeostasis. Lower acylated ghrelin/desacylated ghrelin ratios are associated with better metabolic profiles in patients with schizophrenia treated with olanzapine[57]. Leptin, adiponectin, and ghrelin levels differ significantly in patients with schizophrenia receiving clozapine and olanzapine due to the direct effects of the medications, rather than due to weight gain[58]. Additionally, the leptin/adiponectin ratio seems to be a preferential marker of metabolic syndrome in patients with schizophrenia compared with leptin or adiponectin alone[59].

Orexins, also known as hypocretins, have been suggested to regulate wakefulness, feeding, and metabolic homeostasis[60]. A study found that orexin-A level was elevated in patients with schizophrenia treated with antipsychotics, particularly in those taking fewer obesogenic antipsychotics[61]. The potential protective role of orexin-A against antipsychotic-related metabolic abnormalities may be attributable to the thermogenesis resulting from increased sympathetic tone and reduced peripheral insulin resistance[61].

CCK plays an important role in induction of gallbladder contraction, stimulation of pancreatic secretion, regulation of gastrointestinal motility, and induction of satiety [62]. Studies found that CCK is related to obesity and metabolic syndrome in the general population[63,64]. Animal studies reported that olanzapine could counteract the satiating effect of CCK[65] , and clozapine could reduce hypothalamic messenger RNA of CCK-2 receptor[66]. In contrast, human studies found that CCK level did not change significantly after olanzapine treatment[67,68]. The role of CCK in antipsychotic-induced metabolic disturbances warrants further investigations.

Neurotransmitters

Histamine H_1 receptor antagonism promotes feeding, and the affinity for H_1 receptors is closely correlated with AIWG[69], with clozapine and olanzapine having the highest affinity. Researchers have also proposed that drugs with H_1 receptor antagonism may also induce weight gain because of their sedative effects and consequential reduced mobility[70].

Serotonin is known to provide a satiety signal, and serotonin 5-HT_{2C} receptors are integral to the regulation of energy homeostasis by working together with the melanocortin and leptin signaling pathways[71]. Several SGAs, including clozapine and olanzapine, are potent 5-HT_{2C} inverse agonists and cause significant weight gain. However, ziprasidone, which also has a high affinity for 5-HT_{2C} receptors, is associated with limited weight gain, indicating that no single neurotransmitter system can fully explain AIWG. Conversely, the 5-HT_{1A} receptor exhibits the opposite effect of the 5-HT_{2C} receptor on food intake. The 5-HT_{1A} partial agonism, the common mechanism between aripiprazole, lurasidone, and ziprasidone, may reduce the risk of metabolic disturbances[72].

One study reported that bromocriptine, a specific dopamine D_2 receptor agonist, can counteract antipsychotic-induced hyperphagia and body weight gain in rats[73]. Dopamine D_2 receptor antagonism can enhance the 5-HT_{2C}-mediated effects on food intake and influence glucose metabolism by disinhibiting prolactin secretion[74]. Prolactin, which can stimulate pancreatic β-cell proliferation and insulin production and secretion, may be inversely associated with diabetes mellitus risk[75]. Moreover, prolactin generally suppresses lipid storage and adipokine release[76]. These characteristics may explain the reason that FGAs, risperidone, and amisulpride, which exhibit a higher hyperprolactinemia incidence than do other SGAs, have a lower propensity to develop metabolic disturbances.

Cholinergic muscarinic M_3 receptors are highly expressed by pancreatic β-cells, and low olanzapine and clozapine concentrations, both potent M_3 antagonists, can considerably and selectively impair cholinergic stimulated insulin secretion by blocking muscarinic M3 receptors in isolated rat islet cells[77]. The affinity for the cholinergic muscarinic M_3 receptor is therefore suggested to be the predictor of the propensity of antipsychotic-induced type 2 diabetes mellitus[78].

The support for α1- and α2- adrenergic receptor involvement in the etiology of AIWG is not as well developed as that for the aforementioned receptors. However, evidence indicates that these receptors may be associated with glucose control and may be synergistic with other receptor activities in contributing to AIWG[79].

Numerous pharmacogenetic investigations have identified the role of genetic polymorphisms associated with metabolic disturbances. The most-studied candidate genes that derive from receptors considered to mediate antipsychotic effects on food intake include serotonin 5-HT_{2C}, histamine H1, *ADRA1A*, and dopamine D_2 receptors [80]. Other genes that have been investigated in association with metabolic disturbances include leptin (*LEP*), leptin receptor (*LEPR*), ghrelin (*GHRL*), adiponectin (*ADIPOQ*), insulin-induced genes 1 and 2 (*INSIG1* and *INSIG2*), cannabinoid receptor 1 (*CNR1*), fat-mass and obesity-associated protein (*FTO*), methylenetetrahydrofolate reductase (*MTHFR*), and melanocortin-4 receptor (*MC4R*)[71,81].

Gut microbiota

The gut microbiome can interact with the central nervous system tract through the gut–brain axis. Compared with healthy controls, patients with schizophrenia exhibited a lower gut microbial richness index and diversity index[82]. Several studies have reported an association between metabolic disturbances and gut microbiota in patients with schizophrenia[83,84]. The mechanisms underlying antipsychotic-induced metabolic disturbances mediated through gut microbiota might involve an influence on energy homeostasis and aggravation of chronic inflammation[85,86]. Maier *et al*[87] reported that antipsychotic drugs exhibit antimicrobial activity and may disturb the gut ecosystem. Gut microbiota that may modulate the gut hormone system include ghrelin, peptide YY, glucagon-like peptide-I, and CCK, which play critical roles in adjusting energy homeostasis relative to glucose metabolism, fat storage, and appetite control[85]. Antipsychotic-induced dysbiosis can produce several inflammatory cytokines, including interleukin 1, interleukin 6, and tumor necrosis factor alpha, which are essential in mediating the relationship between gut microbiota and metabolic disturbances[88].

Potential predictors

Several predictors of AIWG and metabolic disturbances have been identified, including female gender and younger age[89]. Debate is ongoing regarding the relationship between baseline BMI and AIWG, even though low-baseline BMI and normal weight status (*i.e.* BMI < 25) have been frequently associated with greater AIWG[90]. Lan *et al*[91] applied artificial intelligence to develop a neurofuzzy model, including physical factors (baseline weight, height, and waist and hip circumferences), lifestyle factors (smoking, dietary patterns, and exercise levels), genetic factors (*ADRA1A*, *ADRB3*, *ADRA2A*, *5-HTR_{2A}*, and *5-HTR_{2C}*), and psychopathology severity as predictor variables, with a 93% prediction rate for weight gains among patients with schizophrenia treated with antipsychotics.

METABOLIC MONITORING

National and international groups have developed guidelines for screening and monitoring AIWG and metabolic disturbances, but studies have indicated that these guidelines are not routinely implemented in clinical care[92]. Table 2 illustrates the comparison between two guidelines proposed by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity[32], and the British Association for Psychopharmacology[93]. Notably, the monitoring frequency should be adjusted according to the clinical situation or after a change in antipsychotic medication.

Lin *et al*[94] developed an artificial neural network and multiple logistic regression models without biochemical parameters to identify rapidly metabolic syndrome in SGA-treated patients. The researchers suggested that waist circumference and diastolic blood pressure were the most predictive variables. Other risk factors for antipsychotic-induced metabolic syndrome should also be evaluated, including smoking, dietary habits, and physical activity levels as well as personal and family history of obesity, diabetes mellitus, and cardiovascular diseases[95].

Table 2 Metabolic monitoring guidelines as proposed by various organizations

	US consensus[32]	BAP guidelines[86]
Weight	At 4 wk, 8 wk, and 12 wk after initiating or changing SGA therapy, then quarterly	BMI weekly for the first 4–6 wk, then every 2–4 wk for up to 12 wk. At a minimum, once every 4 wk for the first 12 wk, then at 6 mo and at least annually
Blood glucose	Assessed fasting plasma glucose at 3 mo, then annually	Assessed fasting or random plasma glucose in the initial weeks and glycated hemoglobin at 12 wk, 6 mo, and then annually
Lipid profile	At 3 mo, then repeated at 5-yr intervals if normal	At 12 wk, 6 mo, and then annually. The total cholesterol/high-density lipoprotein cholesterol ratio should be required.
Blood pressure	At 3 mo, then annually	At 12 wk, 6 mo, and then annually

US consensus: Consensus proposed by American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity[32]; BAP guidelines: Guidelines proposed by the British Association for Psychopharmacology[86]; SGA: Second-generation antipsychotics; BMI: Body mass index.

INTERVENTIONS

The National Institute for Health and Care Excellence guidelines on psychosis and schizophrenia in adults suggest that these patients, particularly when taking antipsychotics, should be offered combined dietary and physical activity programs as well as help for smoking cessation from a psychiatric multidisciplinary care team[96]. Studies have reported that these nonpharmacological strategies for AIWG are beneficial and cost-effective and therefore should be a priority, particularly in early antipsychotic treatment stages[97,98].

Although lifestyle interventions are always crucial, switching to a different antipsychotic medication with a lower propensity for weight gain could also be effective for managing metabolic adverse effects. Studies have shown that switching to aripiprazole, amisulpride, ziprasidone, and lurasidone is beneficial for weight or metabolic measurements[99].

Because switching antipsychotics may result in psychosis decompensation and relapse, another strategy that involves adding adjunctive medication to mitigate weight gain and metabolic changes has been studied extensively. The proposed medications are listed and discussed subsequently.

Metformin

Metformin, probably the most hopeful drug to attenuate antipsychotic-induced metabolic abnormalities[100], is a hypoglycemic drug for treating type 2 diabetes mellitus and employs a mechanism for reducing hepatic glucose production and improving insulin sensitivity without causing overt hypoglycemia. Metformin has also been effective in improving lipid metabolism by reducing triglyceride levels[101].

A meta-analysis of 12 randomized controlled trials (RCTs) concluded that adjunctive metformin is effective in treating AIWG and metabolic disturbances; the doses used in these trials ranged from 500 mg/d to 2550 mg/d[100]. Wu *et al*[102] conducted a RCT to test the efficacy of metformin alone, lifestyle intervention alone, and in combination in 128 first-episode patients with schizophrenia who added > 10% to their weight after receiving antipsychotic medications. After 12 wk, lifestyle intervention alone, metformin alone, and in combination were effective in attenuating AIWG and metabolic disturbances. Lifestyle intervention plus metformin demonstrated the greatest effect on weight loss, whereas metformin alone was more effective for reversing weight gain and increasing insulin sensitivity than lifestyle intervention alone[102].

Topiramate

Topiramate, a medication for epilepsy treatment and migraine prevention, is observed to reduce weight by poorly understood mechanisms likely related to glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonism in the hypothalamus and modulation of hypothalamic concentrations of neuropeptide Y, galanin, and corticosteroid concentrations; topiramate also stimulates lipoprotein lipase and inhibits carbonic anhydrase[103,104]. A meta-analysis of 17 RCTs indicated that 50–400 mg/d adjunctive topiramate significantly reduced weight or BMI and psychopathology in patients with schizophrenia[105].

Amantadine

Amantadine, an antiviral agent for influenza A treatment, has been shown to reduce extrapyramidal adverse effects. Evidence shows that amantadine enhances dopamine release indirectly through antagonism of the N-methyl-D-aspartic acid glutamate receptor[106]. According to a meta-analysis of five RCTs, adjunctive amantadine moderately outperformed placebo in terms of weight reduction[100]. Amantadine augmentation does not seem to exacerbate psychosis and may even be effective in alleviating negative symptoms[107].

Aripiprazole

Aripiprazole, which acts as partial agonist of dopamine D_2 and serotonin 5-HT_{1A} receptors as well as an antagonist of 5-HT_{2A} receptors, is categorized in the group with the lowest propensity for weight gain. A meta-analysis of nine RCTs indicated that adjunctive aripiprazole with SGAs results in significant weight reduction compared with placebo[108]. Reviews have also reported a protective effect of adjunctive aripiprazole with other antipsychotics for dyslipidemia and diabetes mellitus when compared with antipsychotic monotherapy or other antipsychotic combinations[109]. Combining aripiprazole with other low metabolic risk antipsychotics such as ziprasidone, amisulpride, or lurasidone to mitigate weight gain warrants exploration.

Fluvoxamine

Fluvoxamine, a potent cytochrome P450 1A2 inhibitor, blocks the major metabolism pathway of clozapine, resulting in a 5–12-fold increase in plasma clozapine levels and a decrease in the levels of its major active metabolite norclozapine. Norclozapine, not clozapine, is associated with increases in weight and plasma glucose and triglyceride levels[110]. Lu *et al*[111] randomized patients with schizophrenia to receive either 50 mg/d fluvoxamine plus 100 mg/d clozapine or 300 mg/d clozapine. The authors found that the clozapine–fluvoxamine combination significantly attenuated increases in body weight and insulin resistance as well as in insulin, glucose, and triglyceride levels compared with clozapine monotherapy. The combination also significantly reduced psychopathology compared with clozapine monotherapy[111]. As a clinical implication, clinicians should reduce clozapine dosage and carefully monitor clozapine levels if this combination is applied.

SUPPLEMENTAL PRODUCTS

Omega-3 polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation could produce favorable hypolipidemic effects, a reduction in pro-inflammatory cytokine levels, and improvement in glycemia in patients with type 2 diabetes mellitus[112]. Proposed mechanisms by which n-3 PUFAs may counteract metabolic disturbances include modulating lipid metabolism, regulating adipokines such as adiponectin and leptin, alleviating adipose tissue inflammation, promoting adipogenesis, and altering epigenetic mechanisms[113]. According to a meta-analysis of 19 RCTs, adjunctive n-3 PUFAs could improve psychopathology and reduce triglyceride levels in patients with schizophrenia[114].

Melatonin

The efficacy of melatonin in reducing SGA-related metabolic adverse effects is inconsistent. Modabbernia *et al*[115] reported that melatonin was effective in alleviating olanzapine-induced weight gain and hypertriglyceridemia, whereas Agahi *et al*[116] noted that melatonin significantly increased HDL levels and decreased fasting blood sugar levels but increased weight in patients receiving SGAs compared with the placebo group. Romo-Nava *et al*[117] reported that melatonin is effective in attenuating SGA-induced metabolic adverse effects in patients with bipolar disorder but not in patients with schizophrenia. A recent review manuscript reported that adjunctive melatonin therapy has positive outcome for attenuating antipsychotic-induced metabolic disturbances in patients with schizophrenia[118]. Additional studies on the effect of melatonin on antipsychotic-related metabolic side effects are warranted.

CONCLUSION

Studies have demonstrated that antipsychotic drugs potentially induce or trigger metabolic disturbances, which are a major cardiovascular risk factor for patients with schizophrenia. In general, SGAs carry a higher risk of metabolic disturbances than do FGAs. Various SGAs are also associated with varying potentials for weight gain and can be roughly categorized into three groups: Clozapine and olanzapine (highest risk); quetiapine, risperidone, and paliperidone (intermediate risk); and aripiprazole, ziprasidone, and lurasidone (lowest risk).

Notably, Wu and Gau[119] found that patients with schizophrenia and type 2 diabetes mellitus develop few advanced diabetes mellitus complications after receiving regular antipsychotic treatment. The authors proposed that appropriate antipsychotic treatment can improve the patients' conditions and thereby increase the frequency of healthy behavior.

Despite a growing knowledge of the biochemical profiles of antipsychotic agents, the underlying mechanisms of their association with metabolic disturbances remain inconclusive. The binding affinities of antipsychotics to several neurotransmitter receptors, such as H_1, 5-HT_{2C}, 5-HT_{1A}, D_2, M_3, and adrenergic receptors, might be associated with induction of metabolic disturbances. Studies have revealed a positive association between AIWG and therapeutic benefits, particularly in patients treated with olanzapine and clozapine, which suggests that these medications may possess a shared mechanism related to their metabolic liability[120]. Various peptide hormones, including leptin, adiponectin, ghrelin, and orexin, are also suggested to be metabolic disturbance biomarkers. Notably, an increasing amount of evidence indicates that genetic polymorphism has a strong influence on AIWG and metabolic disturbances, further highlighting the complexity and multiplicity of the mechanisms.

Despite established guidelines and recommendations, patients treated with antipsychotic drugs have not adequately received the baseline and follow-up assessments of metabolic and cardiovascular risk factors. Moreover, psychiatrists and members of multidisciplinary care team should motivate patients to pursue healthy lifestyle behaviors, including dietary and physical activity programs. If lifestyle interventions do not succeed, switching to another antipsychotic drug with a low metabolic risk or including an adjunctive medication to mitigate weight gain can be an effective intervention option. All interventions should be adequately monitored, as individual patients may respond unpredictably to any of these pharmacological and natural agents.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 711-735

DOI: 10.5498/wjp.v11.i10.711

ISSN 2220-3206 (online)

REVIEW

Alternative models for transgenerational epigenetic inheritance: Molecular psychiatry beyond mice and man

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Author contributions: Stonehouse SLA, Hime GR and Pang TY prepared the initial draft; Pang TY and Hime GR edited and reviewed the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interests.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin:

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Abstract

Mental illness remains the greatest chronic health burden globally with few inroads having been made despite significant advances in genomic knowledge in recent decades. The field of psychiatry is constantly challenged to bring new approaches and tools to address and treat the needs of vulnerable individuals and subpopulations, and that has to be supported by a continuous growth in knowledge. The majority of neuropsychiatric symptoms reflect complex gene-environment interactions, with epigenetics bridging the gap between genetic susceptibility and environmental stressors that trigger disease onset and drive the advancement of symptoms. It has more recently been demonstrated in preclinical models that epigenetics underpins the transgenerational inheritance of stress-related behavioural phenotypes in both paternal and maternal lineages, providing further supporting evidence for heritability in humans. However, unbiased prospective studies of this nature are practically impossible to conduct in humans so preclinical models remain our best option for researching the molecular pathophysiologies underlying many neuropsychiatric conditions. While rodents will remain the dominant model system for preclinical studies (especially for addressing complex behavioural phenotypes), there is scope to expand current research of the molecular and epigenetic pathologies by using invertebrate models. Here, we will discuss the utility and advantages of two alternative model organisms–*Caenorhabditis elegans* and *Drosophila melanogaster*–and summarise the compelling insights of the epigenetic regulation of transgenerational inheritance that are potentially relevant to human psychiatry.

Key Words: Transgenerational inheritance; Epigenetics; Invertebrate models; *Caenorhabditis elegans*; *Drosophila melanogaster*; Environmental stress

Australia

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 24, 2021
Peer-review started: February 24, 2021
First decision: July 4, 2021
Revised: July 19, 2021
Accepted: August 25, 2021
Article in press: August 25, 2021
Published online: October 19, 2021

P-Reviewer: Pethe P
S-Editor: Fan JR
L-Editor: A
P-Editor: Ma YJ

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Core Tip: Psychiatry research is only beginning to identify the complex epigenetic pathologies across various conditions that may regulate symptomatology. Epigenetics may account for certain conditions that are highly heritable but are not fully accounted for by genetics. Preclinical animal models are a necessary tool to accelerate our understanding of molecular mechanisms and for developing new therapeutic options. Simple behavioural and neurobiological assays combined with high levels of functional gene conservation and rapid generation time in easily genetically manipulated organisms make *Caenorhabditis elegans* and *Drosophila melanogaster* excellent systems to model transgenerational epigenetic inheritance phenotypes.

Citation: Hime GR, Stonehouse SL, Pang TY. Alternative models for transgenerational epigenetic inheritance: Molecular psychiatry beyond mice and man. *World J Psychiatr* 2021; 11(10): 711-735
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/711.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.711

INTRODUCTION

Advances in genomic technologies have led to a rapid increase in the number of known genomic variants linked to human psychiatric illnesses. However, we still know little of the molecular and genetic functions of many of these genes or their mode of inheritance. The wealth of genetic information and experimental techniques associated with laboratory model organisms that have not been traditionally utilised for analysis of psychiatric illnesses provide an untapped resource that promise to revolutionise our understanding of these conditions.

At the turn of the 18th century, the French naturalist Jean-Baptiste Lamarck proposed that environmentally adaptive traits could be acquired by an individual over a lifetime and, more importantly, inherited by their progeny. It was not until the 21st century that Lamarckian theory re-emerged from the shadows of Darwin's theory of natural selection and the principles of genetic inheritance. This recent revival has been driven by growing evidence of unusual inheritance patterns across a wide number of species, which collectively indicate the presence of biological mechanisms that govern how the physical environment, diet and individual experiences not only influence our individual constitution, but the health of our descendants as well. In the past decade, preclinical studies of mammalian models of human disease have uncovered robust evidence of transgenerational shifts in health. However, alternative animal models should be considered as a means of conducting more time- and cost-effective transgenerational research. Here, we summarise recent advances in transgenerational epigenetic inheritance stemming from non-mammalian models that have revealed epigenetic processes potentially relevant to psychiatry. We hope to convince readers that research based on these non-mammalian organisms have the capacity to provide novel insights into the molecular pathologies of different neuropsychiatric conditions.

Epigenetic inheritance drives the adaptation of phenotypic traits and plays a significant role in directing human health outcomes across generations. For example, the accumulation of specific epigenetic modifications is proposed to contribute to the increasing prevalence of cardiovascular and metabolic diseases[1,2]. Separately, epigenetic modifications have been demonstrated in the transgenerational transmission of risk for mental illness, and possibly contributing to the increasing prevalence of a range of psychiatric disorders[3-6]. However, non-mammalian models have also contributed by extending our understanding of the molecular pathologies in human disease. For example, studies of the nematode *Caenorhabditis elegans* (*C. elegans*) have not only provided us enlightening perspectives on the molecular regulation of aging[7,8] but also revealed how stress and nutrition are transgenerational modifiers of progeny survival[9-11].

Briefly, transgenerational inheritance broadly describes the process of a parental generation undergoing experiences and exposures that are subsequently linked to altered phenotypes and behaviours in future generations (in F2s at the very least). Note that the phrase 'intergenerational inheritance' describes transmission that is

limited (or only studied up till) to the very next F1 generation (see Figure 1 for further patrilineal and matrilineal distinctions). While the full spectrum of biological processes underlying transgenerational inheritance is yet to be fully elucidated, a multiplex of epigenetic modifications has been implicated. Importantly, epigenetic inheritance specifically excludes the reorganisation of genome sequence through DNA mutations, and some epigenetic marks are species-specific (further emphasizing the importance of multi-species research). The most widely studied epigenetic modifications include DNA methylation, histone protein modifications (such as methylation, acetylation), as well as short and long non-coding RNAs (sncRNAs and lncRNAs, respectively) that moderate transcriptional activity. Due to space constraints, we refer readers to the following reviews that comprehensively discuss the biochemistry of epigenetic modifications relevant to the neuropsychiatric field[12-16]. The epigenome is subject to modification following exposure to stressors that challenge survival, ranging from environmental (exposure to toxic chemicals)[17] to physical (heat stress) to psychological (fear of predation)[18,19]. We now know that offspring can inherit a range of epigenetic modifications that alters their physical or behavioural traits. Over the past decade, preclinical studies of rodent models of chronic stress[20,21] and trauma[22-24] have demonstrated this phenomenon, but could alternative non-mammalian models of stress offer further insight into the relevant epigenetic pathologies? These tools offer the field of psychiatry the opportunity to clarify the extent to which the risk for mental illness may be moderated by parental or ancestral exposures to such stressors and life events, and understand the molecular mechanisms mediating such forms of transgenerational inheritance. Epidemiological studies have reported a range in heritability of neuropsychiatric disorders (although readers should note that there have been relatively few studies given the challenges of conducting such large-scale research). For example, a high degree of heritability (81%) was initially estimated for schizophrenia (SZ) based on twin studies[25], while subsequent estimates based on the Danish and Swedish populations were comparatively lower at approximately 60%[26, 27]. Those latter studies also estimated that heritability of bipolar disorder (BP) was similar to SZ. However, the potential that epigenetic inheritance moderates the heritability of certain neuropsychiatric conditions has yet to be thoroughly investigated. Of course, in contrast, other psychiatric disorders such as alcohol dependence or major depression display low-moderate degrees of heritability[28] so while those disorders may involve aspects of epigenetic pathology, it is less likely that epigenetic inheritance would be a significant causal factor.

While studies of *C. elegans* and *Drosophila melanogaster* (*D. melanogaster*) may be initially dismissed as far removed from relevance to human physiology, and although most preclinical drug testing is performed with rodent models, these invertebrate model systems provide alternative approaches to conducting complementary research of common epigenetic mechanisms and biochemical processes that may be fundamental to neuropsychiatric pathologies. One should not forget that mammalian transgenerational research can trace its roots to historically rich and revealing studies of plants. Some of the earliest evidence for the phenomenon include Barbara McClintock's ground-breaking studies of retrotransposition in maize and the transgenerational inheritance of transposon phases. While we tend to associate 'stress' with the notion of psychosocial stress, this term can be used to encompass any extrinsic condition that disturbs the normal function of the biological system, or a condition that decreases fitness, including thermal stress, desiccation, UV stress, starvation, chemical exposure and overcrowding. In using alternative animal models, it is crucial that etiologically relevant stressors are applied in the appropriate manner. Heat stress is well known to impact a wide range of physiological and behavioural parameters, which can result in gastrointestinal dysfunction[29], increased blood pressure and disordered metabolic function[30]. In particular, elevated temperatures cause profound disruptions to various aspects of reproduction in both mammals and invertebrates including mating behaviours[31,32], spermatogenesis and oogenesis, egg/foetal development and viability, and offspring body size[33,34]. With mounting concerns about climate change, and recent increases in unusual climate events, understanding how we adapt to such environmental changes and the implications for global population health trends have become more important than ever. A recent systematic review of the impacts of climate change on mental health reported on the complexities in attempting to consolidate the data, but highlighted more common psychopathologies such as anxiety and trauma[35]. It is unclear if and how climatic factors could influence human health outcomes through epigenetic modifications. Understandably, designing and conducting human studies of this nature would be highly challenging due to the inherent complexities *e.g.* having to account for geographical and ethnic diversities. However, research based in the primary

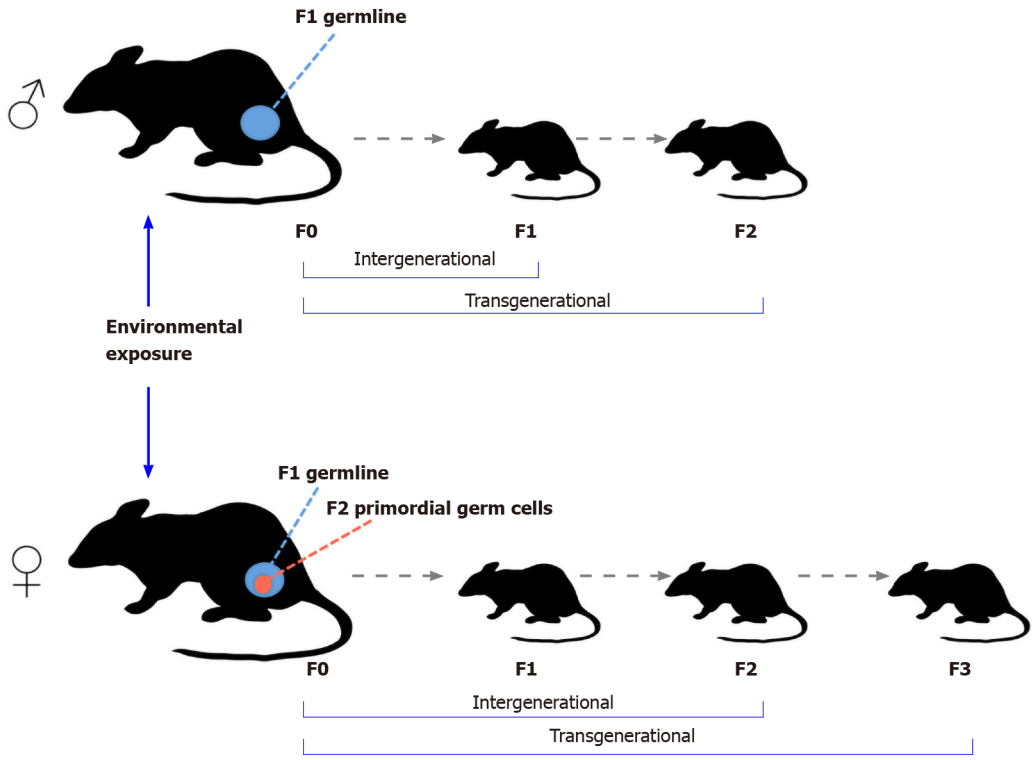


Figure 1 Differences between the definition of transgenerational and intergenerational inheritance through the male and female germ lines.

production industries may be an unexpected source of early clues as to how these occur. Afterall, developing the knowledge to control the effects of heat stress has been crucial to the field of agriculture for maximising crop yield[36,37] and maintaining livestock fecundity and fitness[38,39].

There are mounting calls to recognize that ancestral health is a significant contributing factor of current day human health and phenotypes, and this would require maintaining detailed individual medical records for longitudinal epidemiological studies. On a large scale, such a perspective shift would aid us in identifying the determinants of public health issues and evaluating possible interventions and treatments. Furthermore, elucidating the mechanisms driving environmentally-induced epigenetic changes linked to specific aspects of health and disease may promote a shift towards the development of personalised treatments and drugs based on these signatures[40]. With numerous epigenetic processes conserved from invertebrates to humans, it is unsurprising that many fundamental epigenetic processes are also shared by humans and non-mammalian animals. Therefore, there is valid argument for utilising non-mammalian species as viable alternative animal models to investigate environmentally induced changes in human health, stress response and behavioural adaptations. We will now summarise recent evidence from transgenerational studies of key two non-mammalian models-*C. elegans* and *D. melanogaster*–focussing on environmental stressors and highlight their potential utility for investigating the molecular pathologies of psychiatric conditions.

EPIGENETIC MODIFICATIONS IDENTIFIED BY TRANSGENERATIONAL STUDIES OF *C. ELEGANS* RELEVANT TO PSYCHIATRY

In contrast to mammalian models where multigenerational studies are impeded by long generational times, logistical difficulties and confounding factors, invertebrate models breed rapidly with large progeny cohorts, making them ideal models for performing multi-generational studies. There are the obvious limitations of *C. elegans* as a model, primarily that it is a relatively simple organism lacking many organ systems found in vertebrates. However, the *C. elegans* genome possesses homologs of about two-thirds of all human disease genes. Thus, it is widely used as a model system for studying aging, age-related diseases[41] and neurogenerative conditions[42].

Transgenerational studies of *C. elegans* could therefore provide insight into the molecular pathologies and epigenetic modifications that could be accumulating across generations in humans. Here, we will summarise recent advances in our understanding of the transgenerational responses of *C. elegans* involving thermal stress and starvation and highlight their relevancy to human psychopathologies (Table 1).

The most impressive finding to-date was that exposure of a single progenitor generation to an elevated rearing temperature (25 °C instead of 20 °C) caused transcriptome-wide expression changes that persisted for a further seven generations after temperature normalisation[43]. Importantly, it was identified that the ancestral exposure to a higher temperature was associated with a reduction in the repressive histone modification H3K9me3 (trimethylation of lysine 9 residue in histone H3) in both oocytes and sperm, before onset of zygotic transcription. What could be of importance to the psychiatry field was the revelation that there was de-repression of endogenously repressed repeat sequences, and increased expression of two DNA transposons remained for up to five generations. The role of repetitive elements in human health and disease is still unclear but they have been speculated to be potential etiological factors for SZ, BP and major depressive disorder (MDD)[44], despite a present lack of consistent evidence. For example, there has only been a single report of a repetitive element insertion in three monozygotic twin pairs discordant for SZ[45] but similar observations have not been detected in other studies. However, subsequent studies have reported elevated levels of Class I retrotransposon RNA in cerebrospinal fluid, whole blood and serum samples from SZ patients[46-48]. It should be noted that these latter studies were conducted by the same research group and further independent verification is still required. At the present time, there are also no available rodent models of abnormal repetitive element expression so determining its relevance to neuropsychiatric pathologies is impossible. *C. elegans* would therefore be a prime model organism to investigate environmental factors associated with the aforementioned psychiatric conditions, with the dysregulation of repetitive element expression as a primary outcome measurable. Such studies would either cement their causal roles or establish them as secondary molecular pathologies.

Separately, another repressive histone mark linked to *C. elegans* lifespan[49], di methylation of lysine 9 residue in histone H3 (H3K9me2), has also been implicated in various psychiatric conditions. Increased levels of H3K9me2 were found in post mortem SZ brains and in peripheral blood cells[50]. However, the directionality of this change in expression may vary depending on the specific psychopathology, according to evidence from rodent studies. For example, stress-induced depression was associated with reduced H3K9me2 occupancy at the oxytocin and arginine vasopressin gene promotors, both of which were normalised by physical exercise[51]. Thus, the outcomes linked to the manipulation of H3K9me2 levels are also gene specific. This is further exemplified by the capacity for Cdk-5 targeted H3K9me2 to attenuate cocaine-induced locomotor behaviour and conditioned place preference[52]. These clearly showcase the complexity to epigenetic regulation of gene transcription and the significant challenges faced when attempting to treat psychiatric conditions by targeting a single histone modification. However, armed with precise knowledge of the molecular pathologies, aiming to modify negative behaviours in addiction through gene-targeted histone modification could be an intriguing prospect for the future.

A recent study examined a more severe temperature perturbation through acute heat shock (34 °C for 5 min) and discovered that this caused maternal neurons to release the neurotransmitter 5-HT, which facilitated transcription factor heat shock factor 1 (HSF-1)-mediated mRNA production in soon-to-be fertilized germ cells[9]. The authors proposed that this timely activation of HSF-1 in germ cells ensures viability and future stress tolerance since embryos that arose from heat-shocked mothers contained an excess of protective mRNA and their F1 progeny were more resilient to subsequent temperature insults. It was found that HSF-1 recruited the histone chaperone FAcilitates Chromatin Transcription (FACT) complex to alter histone dynamics and promote transcription of the heat shock protein Hsp70. Interestingly, several studies have identified an accumulation of Hsp70 associated with MDD. In a study of post-mortem brain samples from patients with MDD, Hsp70 was significantly elevated in the dorsolateral prefrontal cortex, while antidepressant treatment did not have any modulatory effect[53]. Separately, elevated serum Hsp70 levels were reportedly predictive of premenopausal women who would go on to develop MDD [54], although Hsp70 levels subsequently decreased for women who did not develop MDD. Collectively, this suggests that Hsp70 could be a useful biomarker for MDD risk but it remains to be verified in a younger, or even a healthy, population.

Table 1 Studies of transgenerational epigenetic inheritance in *Caenorhabditis elegans* of relevance to neuropsychiatric conditions and mammalian preclinical models

Type of stress (if applicable to study)	Transgenerational shifts in progeny phenotypes	Epigenetic modifications implicated in the inheritance process	Ref.	Psychiatric conditions with similar epigenetic pathology	Ref.
Elevated temperature	Temperature-induced transcriptome changes potentially up to F14 generation	Heat shock reduces H3K9me3 to facilitate de-repression of endogenously repressed repeats (DNA transposons)	Klosin *et al* [43], 2017	Repetitive elements as etiological factors for schizophrenia (SZ), bipolar disorder and major depression (review)	Darby and Sabunciyan 2014[44]
		No difference in another repressive mark, H3K27me3		Altered expression of human endogenous retroviruses associated with autism spectrum disorder and SZ (review)	Misiak *et al* [169], 2019
		Active histone marks H3K36me3 and H3K4me2 both unchanged		Tissue-specific repetitive elements expression differences in Parkinson's disease	Billingsley *et al* [170], 2019
Heat shock	Maternal heat shock altered survival of F1 progeny through 5-HT dependent HSF-1 recruitment to heat shock protein gene promotors. Persistence of phenotypic changes not investigated	Histone H3 occupancy at *hsp70* genes decreased following heat shock	Das *et al* [9], 2020	MDD associated with increased hsp70 expression in post mortem dorsolateral prefrontal cortex	Martín-Hernández *et al*[53], 2018
				Elevated serum HSP70 levels predicted development of MDD for premenopausal women. Serum HSP70 decreased over time for women who did not develop MDD	Pasquali *et al* [54], 2018
				Decreased Hsp70 expression in CA4 associated with complete seizure remission for temporal lobe epilepsy	Kandratavicius *et al*[171], 2014
NA	NA	Transgenerational inheritance of H3K36me3 is regulated by two distinct histone methyltransferases, MES-4 and MET-1	Kreher *et al* [172], 2018	H3K36me3 implicated in SZ susceptibility SNPs. But histone lysine methyltransferases yet to be investigated in the context of SZ	Niu *et al*[65], 2019
NA	NA	Lifespan regulated by the H3K9me2 methyltransferase MET-2	Lee *et al* [49], 2019	H3K9me2 elevated in post-mortem SZ brains and peripheral blood cells. Treatment with histone methyltransferase inhibitor BIX-01294 decreased H3K9me2 levels and rescued expression of SZ risk genes	Chase *et al*[50], 2019
				Reduced H3K9me2 at oxytocin and arginine vasopressin gene promotors in a rodent model of stress-induced depression. Rescued by physical exercise	Kim *et al*[51], 2016
				Cdk-5 targeted H3K9me2 attenuates cocaine-induced locomotor behaviour and conditioned place preference in a rodent model of addiction	Heller *et al*[52], 2016
NA	Decline in fertility	H3K4me2 demethylase *spr-5*	Greer *et al* [173], 2014	Treatment with antipsychotic drug olanzapine increased H3K4me2 binding on gene loci associated with adipogenesis and lipogenesis in a rat model	Su *et al*[174], 2020
				KDM5C gene that encodes the H3K4me2/3 histone demethylase linked to autism and intellectual disability	Vallianatos *et al* [175], 2018
Heavy metal (arsenite) stress	Increased resistance to oxidative stress up to F2 generation; no change in reproduction or lifespan	H3K4me3 complex components (*wdr-5.1*, *ash-2*, *set-2*), and transcription factors *daf-16* and *hsf-1*	Kishimoto *et al*[10], 2017	Increased H3K4me3 associated with three *synapsin* gene variants in bipolar disorder and major depression	Cruceanu *et al* [63], 2013
				SZ risk variants are over-represented in association with	Girdhar *et al* [64], 2018

				H3K4me3 in human frontal lobe	
				H3K4me3 implicated in SZ susceptibility SNPs	Niu *et al*[65], 2019
				Increased H3K4me3 associated with increased *Oxtr* gene expression in a rat model of methamphetamine addiction	Aguilar-Valles *et al*[68], 2014
Hyperosmotic stress	Increased resistance to oxidative stress up to F2 generation	Not further investigated in study	Kishimoto *et al*[10], 2017	Relevance to human health presently unclear	
Larval starvation	Increased resistance to oxidative stress up to F2 generation	Not further investigated in study	Kishimoto *et al*[10], 2017	Relevance to human health presently unclear	
Larval starvation	NA	Thirteen miRNAs up-regulated (miR-34-3p, the family of miR-35-3p to miR-41-3p, miR-39-5p, miR-41-5p, miR-240-5p, miR-246-3p and miR-4813-5p); Two miRNAs down-regulated (let-7-3p, miR-85-5p)	Garcia-Segura *et al*[77], 2015	Eight differentially expressed blood miRNAs linked to PTSD. Four up-regulated (miR-19a-3p, miR-101-3p, miR-20a-5p, miR-20b-5p). Four down-regulated (miR-486-3p, miR-125b-5p, miR-128-3p, miR-15b-3p)	Martin *et al*[78], 2017
				Deletion of miR-34 family in mice facilitates resilience to stress-induced anxiety and extinction of fear memory	Andolina *et al*[84], 2016
				miR-34 differentially expressed in induced pluripotent stem cells derived from schizophrenia patients	Zhao *et al*[176], 2015
				miR-34a regulates expression of p73, a p53-family member, that is implicated in neuronal differentiation	Agostini *et al*[86], 2011
Starvation	Increased longevity of progeny up to F3 generation	Inheritance of small RNAs through at least 3 generations.	Rechavi *et al*[11], 2014	miRNAs and rRNAs make up the majority of exRNAs in human plasma	Danielson *et al*[91], 2017
		Small RNAs regulating expression of genes involved in nutrition, metabolic health and lipid transport		1 specific exRNA predicted diagnosis of Alzheimer's disease	Yan *et al*[94], 2020
				exRNAs are potentially involved in the paternal intergenerational influence on offspring metabolic health (mouse model)	van Steenwyk *et al*[93], 2020

HSF-1 activity is also associated with elevated histone H4 protein levels in somatic tissue during development, leading to reduced transcription of mitochondrial complex IV genes and decreased respiratory capacity[55]. While it has not been linked specifically to histone H4 only, a similar role of neuronal heat shock proteins in moderating the response to oxidative stress is evidenced in *D. melanogaster* with increased resistance to oxidative stress and extended organismal lifespan, in addition to ameliorating phenotypes associated with Parkinsonism-type genetic models[56]. Collectively, it emphasizes the conserved association between heat shock proteins, oxidative stress and neuronal damage. However, the precise regulatory roles that histone H3 and H4 proteins provide independently to the overall oxidative stress response remain unclear and warrants further investigation. Mitochondrial dysfunction and the accumulation of oxidative stress are crucial factors in the pathophysiology of MDD[57-59], and biomarkers of oxidative stress are elevated in drug-naïve first episode SZ patients[60]. Thus, there is strong interest in targeting oxidative stress deficiencies in MDD, BP and SZ[61] through antioxidant treatments such as N-acetylcysteine[62]. Future studies could use *C. elegans* to explore the efficacies of various antioxidant compounds in treating heat shock-induced oxidative stress, as well as their underlying modes of action. Studies could also be extended to heat shocking *C. elegans* pre-treated with antioxidants to better understand the epigenetic regulation of 5-HT neurotransmission.

The dysregulation of transcriptional activity is widely reported in a swathe of psychiatric conditions but the causes have yet to be precisely identified. For example, H3K4me3 has been implicated in the pathophysiology of SZ, BP and MDD, with increased H3K4me3 is associated with three *synapsin* gene variants in BP and MDD[63] while SZ risk variants are over-represented in association with H3K4me3 in human frontal lobe samples[64]. The latter is a consistent with a separate study examining H3K4me3 association with SZ susceptibility SNPs[65]. While there have been several independent GWAS studies of SZ, there has yet to be an attempt to reconcile the genomic data with epigenomic variation. That would undoubtedly be a tremendous undertaking, but it could further streamline and identify more robust gene candidates in our attempts to pinpoint the primary molecular pathologies underlying SZ. *C. elegans* could be used to first establish the molecular consequences of such an abnormal epigenetic landscape and resulting transcriptional dysregulation (matched to existing human data), before further behavioural studies are extended to mammalian models. Incidentally, H3K4me3 was identified by Kishimoto *et al*[10] as being involved with the transgenerational adaptations to other forms of environmental stressors aside from thermal stress, namely heavy metal exposure, hyperosmotic conditions, and transient starvation[10]. Following progenitor exposure to all three stressors, there were consistent increases in progeny fitness up till the F2 generation; however only the epigenetic mechanism mediating adaptation to arsenite exposure was further investigated. Unlike the repressive histone modifications mentioned above, H3K4me3 predominantly marks transcriptional start sites and is part of a regulatory complex that facilitates access and assembly of RNA polymerase 2[66,67]. Kishimoto *et al*[10] reported that the genetic components (*wdr-5.1*, *ash-2* and *set-2*) of the H3K4me3 regulatory complex were required to manifest the transgenerational adaptations, implicating histone H3-dependent gene transcription in transgenerational inheritance. Therefore, future work on H3K4me3-regulation transcriptional activity could provide new insight into the molecular pathways affected in SZ, BP and MDD by targeting *C. elegans* homologs of human risk genes for more specific investigations.

Finally, in a rat model of methamphetamine addiction, there was greater H3K4me3 association with the oxytocin receptor gene that corresponded to increased *Oxtr* gene expression[68]. As discussed above, strategies to treat addiction-related molecular pathologies by targeting histone modifications will be challenged by having to account for both active and repressive histone marks. The viability of such interventions and their molecular consequences would be ideally be first tested in *C. elegans* before proceeding to trials in mammalian models.

Malnutrition and starvation at different stages of life have a dramatic impact on mental health. For example, famine exposure *in utero* was associated with an increased risk for mental illness in females, though surprisingly with no apparent significant effect on males[69]. Developmental malnutrition driven by abnormalities in oxidative stress pathways has been linked to an increased risk for SZ and other psychiatric illness later-in-life[70]. Nutrition ultimately dictates metabolic health and more recent studies reported that fasting insulin levels and body mass index at different ages were predictive of at-risk status for psychosis or depression[71], while fasting blood glucose and serum lipid levels predicted suicide attempters in young patients with MDD[72]. At the opposite end of the age spectrum, geriatric deficiencies in micronutrients such as folic acid, thiamine or cobalamin have been linked to worsened mental health symptoms[73,74]. However, careful regulation of nutrition through caloric restriction or fasting has been proposed to be effective in improving symptoms of MDD[75], indicating that dietary interventions where appropriate would benefit patients. This could be particularly important in conditions whereby medications could have unavoidable metabolic side effects[76]. While epidemiological data flags the importance of nutrition for mental health, we continue to have a very poor understanding of this interactive relationship in the absence of evidence of causality and the underlying molecular mechanisms. Human studies of that nature would be severely limited by inherent genetic and cultural heterogeneities within populations, and there would be strong ethical arguments against the manipulation of subjects' diets. These issues are circumvented in studies of *C. elegans* wherein genetic homogeneity is controlled and dietary manipulations are feasible, although as *C. elegans* feed upon bacteria subtle dietary manipulations may be more easily accomplished using the chemically controlled diets that have been formulated for *D. melanogaster*. Transgenerational studies of starvation in *C. elegans* have already been conducted with clear evidence of downstream impacts on progeny fitness. More importantly, these studies have identified epigenetic mechanisms regulating the transgenerational adaptations, and these could potentially be regulating the molecular pathologies driving the malnutrition-related increase in risk for mental illness.

Kishimoto *et al*[10] reported that progenitor larval starvation triggered increased resistance to oxidative stress of two generations of progeny[10] but did not pursue the underlying epigenetic mechanisms and their associated molecular adaptations. However, previously, it was reported that starvation during the early L4 Larval stage altered the expression of 13 miRNAs in *C. elegans*[77]. Of the 13, only 2 were downregulated while the miRNAs of the miR-35 family were most highly upregulated. Being a simple organism, there are only 302 known miRNAs in *C. elegans* compared to over 2000 human miRNAs, so studying their role in transgenerational inheritance and phenotype adaptations is comparatively straightforward. miRNAs are now established to be dysregulated in different human conditions and are the subjects of interest for severe stress-related anxiety disorders such as post-traumatic stress disorder and SZ, as prognostic biomarkers and therapeutic targets. However, their role as epigenetic regulators of pathogenesis are unclear and systematic profiling of individual miRNAs to neuronal circuitry could be one approach to identifying their potential pathogenic roles in psychiatric conditions.

In a cohort study of military combat veterans, 8 differentially expressed blood miRNAs were associated with the diagnosis of post-traumatic stress disorder (PTSD)[78], and their predicted gene targets were implicated in neurotransmission and maintenance of the neural circuitry. Indeed, multiple functional magnetic resonance imaging studies have clearly demonstrated that brain function is compromised in PTSD[79,80]. There is initial evidence to suggest that paternal PTSD may also have the capacity to influence the neural function and behaviour of progeny, and that this is through the inheritance of sperm-borne miRNAs. In the social defeat mouse model of PTSD, both male and female progeny displayed significant anxiety and depression-related behaviours despite themselves not having been subject to stressful interventions[81,82]. It was later independently reported that modelling paternal early life trauma alters sperm miRNAs and exerts significant intergenerational alterations of target genes in the brains of progeny (*e.g. ctnnb1*, catenin β1 in the hippocampus)[22]. Our own studies have extended that line of evidence by demonstrating the transgenerational effects of paternal stress exposure and altered sperm miRNAs resulting in significant expression differences of the imprinted gene insulin-like growth factor 2, *Igf2* in the hippocampus of two generations of progeny[21]. While their downstream target genes may have been discovered to be dysregulated, there is still some controversy regarding the intergenerational inheritance of sperm miRNAs because having altered levels of miRNAs in sperm does not translate to those same miRNAs being dysregulated in offspring brains[23]. Despite the transgenerational implications of paternal PTSD on brain function of their children remaining unknown at this time, a bigger unresolved question is how traumatic stress alters miRNA expression , with one possibility being dysregulation of histone protein modifications and altered chromatin state. Unlike PTSD, which is caused by an external trigger, miRNAs appear to be co-regulated with susceptibility risk genes in SZ. For example, one study has reported an over-representation of miR-9-5p-targeted risk genes while miR-9-2 is located in a genomic region strongly associated with SZ[83]. Given the strong environmental component to both PTSD and SZ, continuing research into stress-induced miRNA changes in *C. elegans* could be used to further our understanding of the relevant environment x gene interactions underlying the molecular pathogenesis of PTSD and SZ. Other miRNAs have been implicated in stress-related disorders such as members of the miR-34 family, which are differentially expressed in induced pluripotent stem cells derived from SZ patients[41,84]. Among these, and consistent with the neurodevelopmental hypothesis of SZ[85], miR-34a is a key regulator of p73 expression, a p53-family member that is implicated in neuronal differentiation[86]. However, causal evidence is lacking to demonstrate that miR-34a is an epigenetic conduit for environmental stress to impact on brain development resulting in a schizotypy brain phenotype. One feasible experiment to propose would be ablating expression of the *C. elegans* homolog of miR-34a or the miR-34 family and study the impacts on neuronal differentiation, development and circuit maturation.

Interestingly, Rechavi *et al*[11] report that progenitor larval starvation was associated with extended longevity in three generations of progeny through the inheritance of small RNAs that regulate genes involved in nutrition, metabolic health and lipid transport[11]. It has been demonstrated in *C. elegans* that extracellular RNAs (exRNAs) are transported from one generation to the next through intracellular vesicles or even as unpackaged extracellular material[87]. The transgenerational effects of paternal stress exposures[21-23] involve altered small non-coding RNA content of sperm transmitted in microvesicles within the male reproductive organs[88,89], but so far this has only been demonstrated in mouse models[90]. Perhaps not so coincidentally, miRNAs are one of two major exRNA species in human plasma (the other

being ribosomal RNAs)[91]. Their presence and relative stability have led to an emerging recognition of their promise as 'liquid biopsies' for diseases, but while early adoption has targeted metabolic pathology[92], the correlation of biofluid exRNA levels with psychiatric conditions remain untested. Interestingly, it was reported that chronic injection of serum from a mouse model of trauma into healthy controls was sufficient to recapitulate the intergenerational impact on offspring metabolism[93]. However, miRNA profiling of the serum content was not performed in that study. Very recently, an investigation profiling exRNAs isolated from the plasma of elderly individuals up to 15 years prior to death revealed that the early presence and progressive increase of phosphoglycerate dehydrogenase (PHGDH) exRNA predicted eventual diagnosis of Alzheimer's disease (confirmed with post mortem pathology testing)[94]. Studies of *C. elegans* could be used to first determine how stress triggers an elevation of circulating exRNAs. Subsequently, given that biofluid screening of exRNAs is already being used to aid diabetes and AD diagnoses, there appears to be untapped potential for this methodology as a presymptomatic screening tool in psychiatry.

Overall, recent studies have demonstrated the complexity of epigenetic responses implicated in the transgenerational responses to progenitor stress exposure. These include histone modifications, dysregulation of DNA repetitive elements and altered expression of non-coding RNAs. These are also molecular processes shared by humans and have been identified as molecular pathologies of various psychiatric conditions. Thus, studying the epigenetic response of *C. elegans* to etiologically relevant environmental stressors and the corresponding physiological and behavioural responses will continue to provide further insight into human molecular psychiatry.

EPIGENETIC MODIFICATIONS IDENTIFIED BY TRANSGENERATIONAL STUDIES OF D. MELANOGASTER RELEVANT TO PSYCHIATRY

D. melanogaster has been established as an invertebrate model organism for studying human neurological disorders due to the remarkable evolutionary conservation of multiple human disease-causing genes. *D. melanogaster* have a higher degree of concordance with humans than *C. elegans*, with 75% of human diseases estimated to have a *D. melanogaster* homologue[95]. While also displaying sexual dimorphism in its physiology and behaviour, *D. melanogaster* have a generational time of only 10-12 d as opposed to approximately 6-9 wk for mice. Thus, in a protracted timeframe and at much lower cost compared to using rodents, multi-generational studies can also be performed to assess transgenerational effects and adaptations of *D. melanogaster* offspring to various environmental stressors. Additionally, a wide range of established transgenic strains, gene manipulation techniques and tools are readily available[96]. Here, we refer readers to several broad reviews discussing the utility of *D. melanogaster* research in advancing the understanding of the complex genetic basis for human traits, psychiatric disorders, neurodegeneration, and for drug discovery and screening[97-100]. Of course, the significant limitations of modelling complex neuropsychiatric conditions in *D. melanogaster* must also be acknowledged. Despite the relative ease in genetic manipulation, neuropsychiatric conditions such as SZ are driven by a combination of multiple genetic and environmental factors, and cannot be simply reduced to and reproduced in single, double or even triple transgenic knockout strains. Furthermore, the myriad of behavioural symptoms requires higher brain function to manifest, for which only mammalian models could be considered as appropriate. However, these reasons should certainly not diminish the utility value of *D. melanogaster* as a high throughput screening tool for basic neuropathological, molecular or epigenetic markers of disease. Most recently, *D. melanogaster* have even been used to model insomnia in order to examine the effectiveness of sleep restriction therapy[101]. However, despite these advantages, transgenerational studies in *D. melanogaster* aimed at examining mechanisms of epigenetic inheritance remain relatively sparse. Yet, the limited research has produced some compelling evidence, nonetheless. In this section, we will summarise key findings by highlighting the transgenerational outcomes of environmental and chemical stress exposures on offspring phenotypes paired with the reported epigenetic processes implicated. We will then flag the neuropsychiatric conditions for which further *D. melanogaster* research could potentially shed new light on the pathological origins.

D. melanogaster are sensitive to the climate and temperature fluctuations[102,103] and have been instrumental in advancing our understanding of the heat stress response. Heat stress-associated deleterious effects on physiology and behaviour are

largely attributed to its denaturing effect on proteins, which undergo abnormal folding, entanglement and unspecific aggregation[104]. In addition to the disruption of singular proteins, heat stress can also disrupt other cellular mechanisms with the culmination of these individual disruptions being cell death[105]. The ubiquitous and highly conserved heat shock response is a complex cascade of different processes, the most central being the transcriptional up-regulation of genes coding for the family of heat shock proteins that were in fact first discovered in *D. melanogaster*[106,107]. In addition to the metabolic and physiological effects on the exposed organism[108,109], selective thermal variations can dramatically shift *D. melanogaster* physical phenotypes such as flight ability over generations (impaired by F2 generation and maintained till the F4 generation) in a sex-dependent manner[110,111]. Thus, imposing a suboptimal ambient environment for survival either by changing the housing temperature or through a transient shift of temperature represents the most etiologically relevant approaches to stressing *D. melanogaster*. These encapsulate studies of both cold tolerance[112] and heat tolerance (discussed in detail below, Table 2), and these allow us to investigate how genetic variation dictates response to the environment or *vice versa*. Research into the transgenerational effects of heat stress in *D. melanogaster* have yielded intriguing and robust evidence of altered offspring physiology and heat stress responses. More importantly, those studies have also revealed epigenetic mechanisms that are of particular interest to psychiatry. Perhaps the most compelling demonstrations of environment-directed modifications of *D. melanogaster* epigenetics resulting in altered gene expression are the transgenerational studies of *white* gene expression following heat stress. The X chromosome residing *white* gene encodes for an ATP-binding cassette transporter that facilitates transport of the eye pigment precursors, guanine and tryptophan (red and brown pigment precursors, respectively) into the developing eyes during pupation[113]. Repression of *white* achieved by inserting the cellular memory module Fab-7 upstream of *white* to enhance chromatin silencing results in the loss of eye pigmentation[114]. Importantly, the Fab-7-mediated silencing process involves recruitment of *Polycomb* Group (PcG) proteins, which are essential in the propagation of chromatin structures and regulate gene silencing through S-phase of the cell cycle[115-117]. The mere developmental exposure to a mildly stressful temperature of 29 °C (typical housing temperature is 25 °C) suppressed Fab-7 expression, resulting in the de-repression of *white* and recovery of red eye pigmentation[118]. Importantly, that de-repression event was heritable down both male and female germ lines up till the F4 generation. That "founder effect" and maintenance of a de-repressed state across multiple generations indicates that inheritance of the temperature-modified chromatin state is maintained by the PcG protein complex. Of relevance to the human epigenome, the PcG protein complexes catalyse the formation and maintenance of the inactive histone mark H3K27me3[118], which as previously mentioned, is widely associated with neuropsychiatric conditions with abnormal histone modification patterns and aberrant gene transcriptional profiles [119]. Yet, the regulation of differentially expressed genes by PcG protein complexes in neuropsychiatric conditions has not been reported. While PcG protein complex function has been of great interest to the oncology field given the tell-tale features of DNA hypermethylation and aberrant transcriptional silencing of tumour suppressor genes[120], a causative role in psychiatric disorders has yet to be established. PcG protein complexes serve as a master regulator of active gene transcription so understanding the intricacies of PcG regulation of chromatin states will be essential if targeting aberrant histone modifications are to be a major therapeutic focus of the future. Aside from changes at the *white* gene locus, the multi-generational effects of heat shock on other behavioural (social interaction, mating) and physiological (metabolic and endocrine health) parameters in *D. melanogaster* are yet to be comprehensively studied. It would be very interesting to investigate if PcG protein complexes also have the capacity to affect the social behaviour, cognition and physical attributes of *D. melanogaster* by manipulating the extent of histone methylation associated with neuropsychiatric risk genes.

Interestingly, and in contrast to the stable inheritance pattern mediated by PcG protein complexes, heat shock-induced de-repression of *white* gene expression involving disruption of the heterochromatin assembly was maintained through three generations of embryos but contingent on repeated exposure of the offspring themselves to heat stress[121]. In that study, the transgenerational effects of heat shock were associated with increased phosphorylation of ATF-2, a member of the CREB/ATF family of transcription factors. Interestingly, levels of phosphorylated ATF-2 are reported to be increased in the ventral parieto-occipital region of post-mortem human brains when comparing between medicated and unmedicated patients with depression[122]; it is unknown if pATF-2 Levels could be predictive of a familial

Table 2 Studies of transgenerational epigenetic inheritance in *Drosophila melanogaster* of potential relevance to psychiatric conditions and mammalian preclinical models

Type of stress (if applicable to study)	Transgenerational shifts in progeny phenotypes	Epigenetic processes implicated in the inheritance process	Ref.	Potentially relevant psychiatric conditions	Ref.
Thermal stress (selection based on intolerance to heat stress)	Reduced ability to fly by F2 generation, maintain through to F4 generation	Epigenetic mechanism not investigated; aspects of stress physiology that affect flight still unclear	Krebs and Thompson [111], 2006	Relevance to human health presently unclear.	
Mild heat stress(embryos maintained at 29 °C)	De-suppression of *white* gene up to F4 generation	Disruption of polycomb group (PcG) protein complex affecting H3K27me3	Bantignies *et al*[114], 2003	Despite multiple reports of altered H3K27me3, the involvement of PcG protein complexes in human psychopathologies has not been established	
Heat shock (flies exposed to 37 °C for 1 h)	De-suppression of *white* gene sustained up to F3 generation required repeated exposure to the same paternal stressor. Gradual return to normal upon removal of heat shock	Disruption of pATF-2 mediated heterochromatin assembly	Seong *et al* [121], 2011	Rat model of chronic stress reported increased ATF-2 gene expression in the frontal cortex of chronically stressed rats, which is decreased following chronic antidepressant treatment	Laifenfeld *et al* [122], 2004
				pATF-2 levels are increased in post mortem samples of unmedicated *vs* medicated patients with MDD. No differences detected for bipolar disorder or schizophrenia	Gourzis *et al* [177], 2012
				Case report of decreased chromosome 1 heterochromatin in FTLD, misdiagnosed as SZ. Altered size distribution of chromosome 1 heterochromatic region in unrelated SZ patients compared to controls	Kosower *et al* [178], 1995
				Risperidone inhibition of heterochromatin formation in human liposarcoma cells *in vitro*, in a process involving PKA signalling; extent of dysregulated heterochromatin in psychosis yet to be explored	Feiner *et al* [125], 2019
				Parental exposure to risperidone led to intergenerational effects on F1 predator avoidance behaviours in zebrafish; potential human effects have not been investigated	Kalichak *et al* [179], 2019
Heat stress (flies raised at 29 °C)	Suppression of BX2 transgene cluster over multiple (50) generations	Paramutation of BX2 *via* maternally inherited piRNAs, triggered by heat stress which resulted in active transcription of piRNAs within that gene locus	de Vanssay *et al*[126], 2012	Paramutation is not regarded as an established epigenetic process in mammals	
				However, readers should be aware of this proof-of-concept study in mice	Yuan *et al* [180], 2015
			Casier *et al* [127], 2019	Paternal transmission of "white-tail-tip" phenotype caused by paramutant allele in mice limited to one generation. Maternal miRNAs and piRNAs regulate (inhibit) germline transmission of paramutation	
				14 piRNAs differentially expressed in AD prefrontal cortex samples *vs* controls	Qiu *et al*[128], 2017
				Sequencing of CSF-derived exosome sncRNA revealed combination of 3 miRNAs and 3 piRNAs detected AD and predicted the conversion of mild–cognitive impaired (MCI) patients to AD dementia. Greater predictive confidence when combining the smallRNA signature with pTau and Aβ 42/40 ratio pathology	Jain *et al*[129], 2019
Forced cohabitation with predator or	Stressed females shift behaviour to laying eggs on	Maternal inheritance of chromosome III and NPF (	Bozler *et al* [136], 2019	Dysregulation of NPY levels in the brain is a key pathophysiology of drug	Gonçalves *et al* [181], 2016

endoparasitoid wasps	food rich in ethanol, and that preference is inherited through five generations	*Drosophila* homolog of NPY) gene locus, reduced NPF expression in the fan shaped body of the adult brain drives ethanol preference		addiction. Manipulation of NPY neurotransmission has potentially beneficial behavioural outcomes, depending on the drug in question	
				NPY is implicated in human alcohol misuse disorders	Mayfield *et al* [137], 2002
				NPY is also implicated in rodent models of alcohol misuse disorder	Mottagui-Tabar *et al* [138], 2005
					Thorsell and Mathe[139], 2017
					Badia-Elder *et al*[140], 2003
					Schroeder *et al* [142], 2005
					Robinson *et al* [141], 2019
Restraint stress	Paternal restraint stress affects epigenome, transcriptome and metabolome of F1 progeny	Stress-induced up-regulation of *Upd3* (*Drosophila* homolog of IL-6) in somatic cells and testes, activating JAK/STAT pathway	Seong *et al* [145], 2020	Metabolic dysregulation in the F1 offspring derived from male breeders exposed to early postnatal stress	van Steenwyk *et al*[146], 2018; van Steenwyk *et al*[93], 2020
		Subsequent p38 activation results in dATF-2 deactivation in germ cells leading to decreased H3K9me2 (repressive mark) at target genes. Repressive histone marks inherited by F1 progeny		Review of epigenetic mechanisms proposed to underlie intergenerational transmission of paternal trauma	Yehuda and Lehrner[182], 2018
				Childhood adversity associated with altered DNA methylation of HPA axis and immune system genes; potentially inherited by offspring	Bick *et al*[154], 2012
Methylphenidate (MPH) treatment	Behavioural response to MPH is genetically variable and intergenerational effects can be observed in F1 offspring	Mechanism is unknown but MPH resulted in alterations to expression of many histone modifying genes	Rohde *et al* [158], 2019	ADHD is highly heritable, but the reasons are unclear despite the identification of candidate genes. Future studies should attempt to identify transgenerationally heritable epigenetic modifications as the basis for genetic vulnerability	
				Non-human primate studies indicate that MPH treatment affects normal puberty. The transgenerational implications of this finding for humans needs to be followed-up	Mattison *et al* [155], 2011
G418 treatment (toxic stress)	Exposure of F0 females to G418 resulted in reduction of *Polycomb* group gene expression in up till F3 generation	Maternal *Polycomb* group expression in early embryogenesis affects expression of the zygotic genome, which can be inherited	Stern *et al* [168], 2014	G418 has been successfully used to rescue PTC deficiencies in a cell culture model for frontotemporal dementia. However, its broader utility for treating neuropsychiatric conditions remains unknown	Kuang *et al* [164], 2020
				PTC mutations of neuronal *UPF3B* gene associated with nonspecific mental retardation with or without austism	Laumonnier *et al*[183], 2010

PTC: Premature termination codon; IL: Interleukin.

history of MDD or other forms of stress-related psychopathology. The *D. melanogaster* ATF-2 is known to be an essential regulator of heterochromatin assembly through its co-localisation with HP1, a crucial adaptor molecule for DNA methyltransferases that are recruited along the heterochromatin assembly by H3K9me marks. Thus, despite the lack of evidence at this time, it has been speculated that the general disruption of gene expression in psychiatric conditions such as SZ involves a combination of abnormal DNA methylation and histone methyltransferase activity[123,124], and that recurring environmental stress could be key triggers for the familial manifestations of psychosis. It is especially important that this aspect of epigenetic pathology be examined given more recent *in vitro* evidence that antipsychotics such as risperidone

have the capacity to inhibit heterochromatin formation[125].

Studies of heat stress have also uncovered other heat-induced epigenetic responses involving paramutation and the resulting transgenerational inheritance of small non-coding RNAs *via* the maternal lineage. de Vanssay *et al*[126] described a paramutation event involving P-transposable-element repression in the germ line (termed trans-silencing effect, TSE) that converted other homologous clusters typically incapable of TSE into strong silencers[126]. The transgenerational effects of this paramutation persisted through 50 generations of progeny and was found to specifically require *aubergine* gene-mediated piRNA biogenesis but not Dicer-2 mediated siRNA production. Interestingly, this paramutation is triggered by heat stress and the pattern of piRNA up-regulation is transmitted *via* the maternal lineage[127]. Thus, one of the persistent epigenetic modifications in response to stress in humans could be the emergence of actively transcribed piRNA loci. While piRNAs are not a core focus of molecular psychiatry, piRNAs have started to gain attention in the domain of neurodegenerative diseases after having been found to be differentially expressed in prefrontal cortical tissue of post-mortem AD brains[128]. That has led to questions of their role in disease pathogenesis and the possibility of using them as a reliable biomarker for human disease. In support of the latter notion, miRNA and piRNA profiling of human cerebrospinal fluid-derived exosomes has more recently been proposed to have utility in diagnosing AD, as well as predicting the conversion from mild cognitive impairment to AD dementia[129]. There is sexual dimorphism in the clinical manifestation of AD with more women than men being diagnosed and maternal transmission is more frequently observed than paternal transmission[130]; but the potential involvement of maternally inherited miRNAs or piRNAs to confer AD risk is completely unknown at this time. In *D. melanogaster* it has been established that piRNAs are maternally inherited and aging is associated with an increased presence of novel heterochromatic-only secondary piRNAs[131-134]. However, evidence of a similar pattern of inheritance role in humans has yet to be discovered. Our understanding of piRNA in the context of psychiatry and behaviour is barely in its infancy, and there remains much to be uncovered regarding the piRNA pathogenesis and its direct consequences across the range of neuropsychiatric diseases. Perhaps further studies in *D. melanogaster* can uncover novel piRNA-mediated disease mechanisms for psychiatry conditions that are skewed to maternal transmission.

Predator stress is another form of environmental stress that applies to *D. melanogaster* and studies have revealed that it is sufficiently severe to induce shifts in reproductive behaviours. Females housed in cohabitation conditions with endoparasitoid wasps develop a preference to lay eggs on ethanol-rich food as ethanol protects the larvae from wasp infection[135]. That change in oviposition behaviour was found to be driven by neuropeptide F (the *D. melanogaster* homolog of Neuropeptide Y, NPY) and persisted despite removal of the endoparasitoid wasps. More impressively, a recent study reported that exposure to predatory wasps is also an environmental stressor that triggers a similar transgenerational modification of egg laying behaviour over five generations[136]. That shift towards ethanol-rich substrates was established to be superficially maternally transmitted and involved inheritance of Chromosome III within which resides the *NPF* gene that is differentially expressed in the fan shaped body of the adult female brain. Here, it is worth noting that NPY is of major interest to substance misuse disorders and has been implicated in human alcohol use disorder [137-139] as well as in rodent models[140-142]. Since genetic vulnerability remains the core disease-causing factor for humans, and given that unbiased genetic screening, QTL analyses or GWAS studies are easily paired with functional studies in *D. melanogaster*[143,144], the latter presents as a viable alternative organism to study gene-environment interactions and the triggers that drive alcoholism, with perhaps the next step being a pursuit of the epigenetic mechanisms underlying those pathologies.

Interestingly, by using restraint stress to model strong psychological stress, Seong *et al*[145] found that paternal stress altered the epigenome, transcriptome, and metabolome in a dATF2 pathway-dependent manner[145]. A host of genes involved in metabolic health (amino acid metabolism, glycolysis, TCA cycle) were differentially expressed in the F1 offspring, which is consistent with the observations of similar paternal stress studies in mice[93,146]. The intergenerational effects in *D. melanogaster* were proposed to be caused by stress-induced up-regulation of *Upd3* gene in the testes [the *D. melanogaster* homolog of the pro-inflammatory cytokine Interleukin-6 (IL-6)], which was confirmed by overexpression studies of *Upd3* in paternal somatic cells with corresponding studies of the offspring outcomes. The overall intergenerational effects were proposed to be mediated by stress-induced increases in Upd3 that causes abnormal phosphorylation of dATF-2 in *D. melanogaster* germ cells, resulting in decreased H3K9me2 repressive marks that are inherited by the F1 offspring to

ultimately disrupt heterochromatin assembly and gene transcription. In humans, it remains to be clarified whether IL-6 (or other pro-inflammatory cytokines) correlates with sperm DNA damage[147,148]. However, it is well-established that inflammation has a significant role in the pathogenesis of various neuropsychiatric conditions including MDD[149-151] and SZ[152,153]. It would be interesting to elucidate the relationship of SNPs and risk gene loci with H3K9me2 repressive marks, and its contribution to the development of those conditions especially in familial cases. Additionally, given initial evidence suggesting that traumatic stress has long-term epigenetic consequences including altering the DNA methylation patterns of genes relevant to HPA axis function and the immune (inflammation) response[154], future *D. melanogaster* studies should also focus on DNA methylation as a key epigenetic mechanism mediating the transgenerational inheritance of stress-induced pathologies.

Methylphenidate (Ritalin) is a frontline prescription psychostimulant for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. The increasing frequency of prescription has been the cause for concern regarding over-prescription and overdiagnosis. Methylphenidate treatment has been reported to result in significant developmental delay to puberty with hormonal imbalance in non-human primates[155]. While the impacts on spermatogenesis or sperm health were not investigated in that study, separate work on the major metabolite of methylphenidate, ritalinic acid, has found a significant increase of human sperm motility and viability *in vitro*[156]. However, any effects of long-term methylphenidate treatment on pubertal growth, sperm development *in vivo* and the sperm epigenome are unknown presently. *D. melanogaster* studies have contributed tremendously to advancing our understanding of the genetics of neuropsychiatric conditions. A prime example is they have been used to identify ADHD candidate genes[157] and to determine the transcriptomic response to methylphenidate, which correlate to their locomotor responses to drug treatment[158]. The latter study also identified putative candidate genes through whole genome transcriptomic analysis that accounted for the variability in drug response. Collectively, that body of work establishes *D. melanogaster* as a valid organism to further probe the transgenerational effects of methylphenidate exposure on male reproductive health and progeny behaviours. The aetiology of ADHD remains poorly understood but epidemiological data indicates approximately 80% heritability for both adults and children[159,160] despite only 22% of the disease liability being linked to common gene variants[161]. Given that knockdown of *D. melanogaster* homologues of ADHD candidate genes produces abnormal locomotor phenotypes that are also responsive to treatment by ADHD prescription compounds [162,163], *D. melanogaster* would continue to serve as an ideal organism for future investigations into the epigenetic factors underlying the high degree of heritability of ADHD.

Recently, one study investigating new therapeutic options for treating fronto-temporal dementia (FTLD)[164] explored the use of aminoglycosides–a class of gram-negative bacilli antibiotics that have the capacity to induce eukaryotic ribosomal readthrough of premature termination codon (PTC) sequences to yield a full-length protein. Aminoglycosides have successfully been used to treat various diseases involving PTC mutations such as cystic fibrosis[165], Duchenne muscular dystrophy [166] and Rett syndrome[167], but have yet to be employed for neuropsychiatric conditions. In using a cell culture screening assay to conduct proof-of-principle studies with non-sense mutations of *progranulin* associated with FTLD, Kuang *et al*[164] identified two aminoglycosides that rescued the expression of the *progranulin*. It is worth noting that one of those aminoglycosides, G418 (also known as geneticin), has previously been reported to exert transgenerational effects on maternal *Polycomb* levels in *D. melanogaster* F2 embryos that persisted into the F3 generation[168]. Importantly, G418 exposure lead to growth retardation and delay in pupation times. While the transgenerational implications of G418 would be minimal since FTLD is associated with advanced aging, we believe it is important that readers be aware of such potential risks to offspring should aminoglycosides continue to be explored as therapeutic options for conditions in a younger fertile population.

CONCLUSION

Looking towards the future, improving the prospects for neuropsychiatric patients requires the field of psychiatry to have a more comprehensive understanding of the causes of various conditions, especially regarding how basic molecular and epigenetic pathologies interact and contribute to the overall disease phenotype. A major step

would be the incorporation of epigenome profiling since it is the key molecular intermediary linking genetics (susceptibility) to the environment (stress-related triggers). In highlighting the key findings of studies of *C. elegans* and *D. melanogaster*, we hope readers can come to appreciate the value of conducting basic research employing these two key non-mammalian organisms to potentially uncover novel molecular and epigenetic pathologies. Multiple stress-induced epigenetic modifications that affect the individual have significance in a variety of human neurological conditions, but further findings that progeny are also transgenerationally affected will have broader implications for health projections for future generations. At a time when stress (physical and mental) is prevalent and largely unavoidable, there is great urgency to understand the current mental health crisis and work towards new approaches for treatment and prevention. Of course, it is openly acknowledged that complex human behavioural responses and adaptations related to psychopathologies cannot be modelled in simple organisms. However, many fundamental molecular mechanisms that regulate neuronal behaviour have been conserved across phyla, and those molecular and neuronal circuitries can be interrogated in a rapid manner in simple model organisms Therefore, invertebrate research should be regarded as being tremendously beneficial and highly complementary to human and mammalian model research, and further investments should be made in this regard. An expanded combination of clinical studies, rodent models and molecular studies in model organisms provides an extremely powerful multi-tiered approach to understanding the molecular basis of psychiatric disorders. Focusing on the epigenetic pathologies associated with neuropsychiatric conditions will undoubtedly lead to the development of novel approaches for treatment.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 736-753

DOI: 10.5498/wjp.v11.i10.736

ISSN 2220-3206 (online)

REVIEW

Antipsychotics cardiotoxicity: What's known and what's next

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Author contributions: All authors participated sufficiently in the work to take public responsibility for its content; Li XQ and Tang XR drafted the paper; Li LL conceived the original idea, and drafted and edited the manuscript; all authors provided final approval of the version that was submitted; Li XQ and Tang XR had equal contributions and should be considered as co-first authors.

Supported by National Natural Science Foundation of China, No. 82070285 and No. 81701861.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

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Abstract

Chronic use of antipsychotic medications entails a dilemma between the benefit of alleviating psychotic symptoms and the risk of troubling, sometimes life-shortening adverse effects. Antipsychotic-induced cardiotoxicity is one of the most life-threatening adverse effects that raises widespread concerns. These cardiotoxic effects range from arrhythmia to heart failure in the clinic, with myocarditis/cardiomyopathy, ischemic injuries, and unexplained cardiac lesions as the pathological bases. Multiple mechanisms have been proposed to underlie antipsychotic cardiotoxicity. This review aims to summarize the clinical signs and pathological changes of antipsychotic cardiotoxicity and introduce recent progress in understanding the underlying mechanisms at both the subcellular organelle level and the molecular level. We also provide an up-to-date perspective on future clinical monitoring and therapeutic strategies for antipsychotic cardiotoxicity. We propose that third-generation antipsychotics or drug adjuvant therapy, such as cannabinoid receptor modulators that confer dual benefits — *i.e.*, alleviating cardiotoxicity and improving metabolic disorders — deserve further clinical evaluation and marketing.

Key Words: Antipsychotics; Cardiotoxicity; Sudden cardiac deaths; Cannabinoid receptor; Adrenoceptor

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Core Tip: Antipsychotic drug-induced cardiotoxicity is troubling and sometimes life-threatening, which restricts their clinical application. Herein, we summarize the clinical signs and pathological changes of antipsychotic cardiotoxicity and introduce recent progress in understanding the underlying mechanisms at both the subcellular organelle level and the molecular level. Future perspectives regarding clinical monitoring and therapeutic strategies for antipsychotic cardiotoxicity are also discussed.

s/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 24, 2021
Peer-review started: February 24, 2021
First decision: July 4, 2021
Revised: July 8, 2021
Accepted: September 2, 2021
Article in press: September 2, 2021
Published online: October 19, 2021

P-Reviewer: Akkaya C
S-Editor: Gao CC
L-Editor: Wang TQ
P-Editor: Li X

Citation: Li XQ, Tang XR, Li LL. Antipsychotics cardiotoxicity: What's known and what's next. *World J Psychiatr* 2021; 11(10): 736-753
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/736.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.736

INTRODUCTION

The use of antipsychotics is an important and integral part of psychiatric care and often lasts for a lifetime. Antipsychotics are primarily prescribed for the treatment of schizophrenia and other psychotic diseases[1] and are commonly categorized as first-generation antipsychotics (FGAs, or typical antipsychotics) and second-generation antipsychotics (SGAs, or atypical antipsychotics). Recently, several new and emerging antipsychotic medication strategies, termed third-generation antipsychotics (TGAs), have been marketed or are under clinical development for the treatment of mental disorders[2]. Generally, the evolution of antipsychotics has largely improved therapeutic outcomes in the clinic. However, inevitable side effects remain a clinical limitation that unfortunately results in drug withdrawal or discontinuation of potentially successful regimens[3]. These toxic effects range from minor issues (*e.g.*, mild sedation or dry mouth) to troubling issues (*e.g.*, weight gain or metabolic disturbances) to even life-threatening issues (*e.g.*, cardiotoxicity).

Clinical statistics have reported a clear link between the use of antipsychotics and increased incidence and mortality of sudden cardiac death (SCD)[4]. In a large Danish retrospective study, the incidence of SCD was 14.8 deaths per 100000 person-years in psychiatric individuals[5]. Current users of FGAs and SGAs had higher rates of SCD than nonusers of antipsychotic drugs, with adjusted incidence-rate ratios of 1.99 [95% confidence interval (CI): 1.68 to 2.34] and 2.26 (95%CI: 1.88 to 2.72), respectively[6]. Autopsy-based evidence also confirmed that approximately 3.5% of schizophrenia patients under antipsychotic use died from cardiac causes[7]. Moreover, SGAs seem to predispose patients to a mildly higher risk of SCD than FGAs, with an incidence-rate ratio of SGAs to FGAs of 1.14 (95%CI: 0.93 to 1.39). The incidence of antipsychotic-induced SCD is also dose-related. The incidence-rate ratios of FGA users increased from 1.31 (95%CI: 0.97 to 1.77) for those taking low doses to 2.42 (95%CI: 1.91 to 3.06) for those taking high doses ($P < 0.001$). Among users of SGAs, the incidence-rate ratios increased from 1.59 (95%CI: 1.03 to 2.46) for those taking low doses to 2.86 (95%CI: 2.25 to 3.65) for those taking high doses ($P = 0.01$)[6].

In recent decades, our knowledge of antipsychotic cardiotoxicity has been increasingly improved. This review aims to provide an up-to-date summary of recent progress in understanding the clinical manifestations, pathological alterations, and cellular and molecular mechanisms underlying this critical issue. We also propose future perspectives that await implementation.

CLINICAL MANIFESTATIONS OF ANTIPSYCHOTICS CARDIOTOXICITY

Multiple studies have reported antipsychotic cardiotoxicity from clinical perspectives. These cardiovascular effects range from heart rate (HR) changes and blood pressure (BP) alterations to more severe and fatal issues such as QTc prolongation and congestive heart failure. These manifestations and their closely associated drugs are illustrated in Figure 1.

Heart rate changes

Tachycardia: Antipsychotic agents have anticholinergic properties and thus could cause cardiovascular side effects when vagal tone is significantly decreased by antagonism of type 2 muscarinic receptors. The anti-muscarinic effects include sinus tachycardia and other systemic anticholinergic effects, such as dry mouth, constipation, and urinary retention. Antipsychotic-induced tachycardia is most commonly observed in low-potency FGAs (*e.g.*, chlorpromazine and thioridazine) and some SGAs (*e.g.*, clozapine). Compared with an average of 72 ± 14 beats/min in 42 unmedicated controls, the mean HR significantly increased to 83 ± 14 beats/min in the 111 patients receiving FGAs. It has been estimated that an increase in HR of 10-15 beats/min could be observed in 1/4 of patients taking clozapine. Consistently, data showed that treatment with clozapine (21 d under 200-600 mg/d), haloperidol (18 d

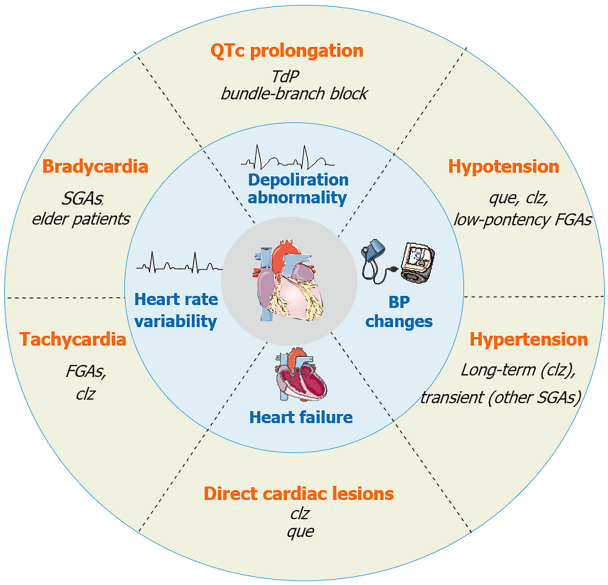


Figure 1 Summary of clinical manifestations of antipsychotic cardiotoxicity. Typical characteristics for each manifestation are concisely listed in black texts. SGA: Second-generation antipsychotic; FGA: First-generation antipsychotic; TdP: Torsades de pointes.

under 5-10 mg/d), and olanzapine (17 d under 5-20 mg/d) increased patients' HRs to 107, 86, and 89 beats/min, respectively, which were significantly higher than those of their matched control subjects (62 beats/min)[8]. Of note, clozapine-induced tachycardia does not seem to be dose-dependent. In a rat model receiving different doses of clozapine administration, a low dose (1.5 mg/kg) and a high dose (5 mg/kg) of clozapine increased the HR by 51 ± 8 and 47 ± 15 beats/min, respectively[9]. This effect was distinct from those of haloperidol and risperidone[8].

Most patients may develop milder tachycardia with drug treatment extension, a phenomenon referred to as drug tolerance, with clozapine being the sole exception. Clozapine-induced tachycardia may be persistent and requires the addition of β-adrenergic receptor antagonists to avoid severe cardiovascular effects for symptomatic patients with HRs over 110-120 bpm[10]. In addition, antipsychotic-induced tachycardia may increase myocardial oxygen demand and aggravate cardiac ischemia in patients with basic cardiovascular diseases. Persistent tachycardia may also contribute to cardiomyopathy[11]. All of these outcomes mandate clinical interventions.

Bradycardia: Some cases also reported antipsychotic impacts on lowering the HR, particularly SGAs such as risperidone[12], quetiapine[13], amisulpride[14], olanzapine [15], and paradoxically clozapine[16]. These cases were mostly elderly patients with signs abated after discontinuation of drugs. It has been reported that risperidone induced bradycardia in an 82-year-old woman (43 beats/min) and 69-year-old man (39 beats/min). Prompt initiation of appropriate resuscitative and supportive measures, along with discontinuation of the offending medication, led to clinical improvement [12]. Quetiapine-induced bradycardia has also been reported in elderly patients, in which settings, a time sequential improvement was achieved after decreasing the drug dosage[13]. A male patient developed symptomatic bradycardia during usage of amisulpride (400-800 mg/d), which dramatically improved after the complete termination of amisulpride usage[14]. An 84-year-old patient presented with conscious depression, bradycardia (40 beats/min), hypotension, miosis, and hypothermia after 2.5 mg/day olanzapine therapy, and his condition improved with supportive therapy [15]. Clozapine also induced bradycardia in elderly patients[16], albeit with more reports of clozapine-induced tachycardia.

Antipsychotics-induced bradycardia may be explained by age-related changes in the pharmacokinetics and pharmacodynamics of drugs in older patients that increase their susceptibility to the side effects of psychotropic medications[16]. The antipsychotic-induced slowdown of HR may lead to more severe outcomes, such as cardiac arrest and SCD. It is hence strongly suggested that clinicians remain vigilant for the signs or symptoms of adverse effects such as bradycardia in their elderly patients who take SGAs.

Blood pressure

Hypertension: In a 24-wk follow-up study, only four (22%) of the 18 patients fulfilled the criteria for hypertension at baseline levels. However, 12 (67%) in 18 patients developed hypertension ($\chi^2 = 6.25$, $df = 1$, $P = 0.0124$) with regard to both systolic BP (SBP) and diastolic BP (DBP) during clozapine treatments[17]. Consistently, a 5-year follow-up observation of 82 patients showed significant increases in SBP ($P = 0.0004$) and DBP ($P = 0.0001$) after clozapine therapy. In these patients, 27% developed hypertension, the rate of which significantly surpassed that in FGA therapy (4%) or in other SGA (olanzapine and risperidone) therapies (9%)[18].

Interestingly, clozapine tended to reduce SBP in the early period after drug initiation, whereas olanzapine and risperidone raised SBP to a statistically significant degree within 3 d of initiation[19]. Aripiprazole, another SGA, was also observed to induce arterial hypertension shortly after drug initiation in two geriatric patients[20]. Both somatic and psychiatric outcomes were favorable after discontinuation of aripiprazole or the introduction of FGAs.

Orthostatic hypotension: Orthostatic hypotension is one of the most common cardiovascular adverse effects of antipsychotics and is more common in elderly patients[21,22]. In a cardiovascular health study enrolling 5201 patients over 65 years old, the prevalence of asymptomatic orthostatic hypotension was 16.2% to 18%, although only 2% were symptomatic[23]. The risk of orthostatic hypotension associated with antipsychotics is increased in patients with autonomic nervous system diseases and fluid imbalance and in those taking concomitant drug therapy that affects hemodynamic tone. Elderly individuals taking multiple medications, such as antipsychotics and hypotensive drugs, constitute a higher risk factor for symptomatic orthostatic hypotension. The incidence of FGA-induced orthostatic hypotension is approximately 77% compared with only 15% in patients receiving placebo[24], with the accepted mechanism being α1 adrenergic blockade and other putative mechanisms such as calcium blockade, inhibition of centrally mediated presser reflexes, and negative inotropic effects[25]. Low-potency phenothiazine antipsychotics (*i.e.*, chlorpromazine and thioridazine) are generally considered the most common FGAs that cause orthostasis[26].

Unlike FGAs, most SGAs, with the exception of clozapine and quetiapine, are less likely to cause orthostatic hypotension due to their low affinity for α_1-adrenergic receptors[26]. Based on available data, the hierarchy of hypotension production was quetiapine (27%) > clozapine (24%) > iloperidone (19.5%), compared with 8.3% in patients taking placebo, while other SGAs (*i.e.*, risperidone, olanzapine, and ziprasidone) barely cause orthostatic hypotension[26,27]. Of note, orthostatic hypotension is dose-dependent and transient. The long-term effect of SGAs may be more associated with hypertension, as mentioned above. Therefore, orthostatic hypotension can frequently be overcome with close monitoring and conservative dosing[28].

Ventricle repolarization abnormalities

QT prolongation: Antipsychotic agents are commonly correlated with repolarization abnormalities, which manifest as iatrogenic prolongation of the QT interval. The QT interval is measured on the electrocardiogram (ECG) from the beginning of the QRS complex (initial deflection or Q wave) to the end of the T wave, which reflects depolarization and repolarization of the ventricles, respectively[29]. An imbalance in ion flow across the cell membrane, especially potassium current impairment, can result in delayed repolarization manifesting a prolonged QT interval[30]. Since this interval is inversely proportional to HR, the QT interval is typically corrected for HR (QTc). The QTc interval in healthy people ranges from 380 ms to 450 ms under the combined impact of age and gender. Some antipsychotic medications are associated with the prolongation of QTc interval (> 450 ms in men and > 460 ms in women). In a cohort study enrolling 4825345 patients, approximately 40% were prescribed an antipsychotic medication and later presented with QTc prolongation[31]. In particular, the Pfizer 054 study conducted by Pfizer Inc. reported the order of QTc interval elongation to be thioridazine (35.6 ms), ziprasidone (20.3 ms), quetiapine (14.5 ms), risperidone (11.6 ms), olanzapine (6.8 ms), and haloperidol (4.7 ms)[32,33]. The U.S. FDA has therefore increased concerns of this serious issue; five different medications have been withdrawn from the market, and several others have received different kinds of product warnings[34].

It is noteworthy that although most antipsychotics are associated with QTc prolongation, it is rather difficult to rank the risk of malignant arrhythmia for the individual antipsychotic drug since ECG measurement methods vary across studies. A

recent clinical review therefore integrated pharmacovigilance data from several international databases. Data from various authorities on the risk of arrhythmia associated with psychotropic medications were weighted and categorized into three risk categories. Aripiprazole, olanzapine, perphenazine, and zuclopenthixol were categorized as class A drugs [no risk of QTc prolongation or torsades de pointes (TdP)]. Amisulpride, chlorprothixene, clozapine, flupentixol, levomepromazine, paliperidone, quetiapine, risperidone, and sulpiride were categorized as class B drugs (a drug with a propensity of QTc prolongation). Finally, haloperidol, pimozide, sertindole, and ziprasidone were categorized as class B* drugs (a drug with pronounced QTc prolongation, documented TdP cases, or other serious arrhythmias) [35].

Serious conduction abnormality: QT prolongation is associated with ventricular arrhythmias, specifically TdP, and SCD. TdP can be inherited (congenital long-QT syndrome, LQTS) or acquired, with the most common reason being medications[36]. The following conditions increase the risk of drug-induced TdP: (1) Disease states/electrolyte levels (heart failure, structural cardiac disease, bradycardia, and hypokalemia); (2) pharmacogenomic variables (presence of congenital LQTS, subclinical ion-channel mutations, and history of or having a relative with history of drug-induced long QT/TdP); and (3) pharmacodynamic and kinetic factors (high doses, women, being elderly, metabolism inhibitors, combining two or more QT prolonging drugs, drugs that prolong the QT and increase QT dispersion, and drugs with multiple actions on ion channels)[37]. Until now, QT prolongation has remained the most extensively used surrogate marker for TdP, while the existing means for precisely measuring prolongation have been debated[38,39]. Moreover, TdP is known to occur at therapeutic doses of SGAs when the QTc interval is < 500 ms. Thus, establishing a clinically standardized threshold of the QTc interval is difficult but important.

Serious conduction system alterations also include right and left bundle-branch block (RBB and LBB) and partial or complete atrioventricular block. It has been reported that an abnormal cardiac conduction system was the second most common cause of death in 24 patients dying suddenly from long-term antipsychotic use[40]. The main mechanisms are antipsychotic-induced pericarditis involving the sinus node, atrial muscle, and atrioventricular node or endocarditis involving the RBB, LBB, and Purkinje fibers.

Heart failure

Antipsychotic-induced heart failure is a consequence of prior direct cardiac lesions in response to drug stimuli. These pathological lesions included myocarditis, cardiomyopathy, ischemic heart diseases (IHD), *etc.*[41].

Currently available reports have mainly linked clozapine with an increased risk of heart failure. A psychiatric patient on chronic low-dose clozapine (75 mg/d) therapy presented with congestive heart failure secondary to the cardiotoxic effects of psychiatric medication, a condition that failed to be corrected by conventional heart failure treatments. Drug discontinuation is commonly issued when confronting clozapine-induced heart failure[42]. An exclusive report also presented the case of a 37-year-old woman who developed cardiomyopathy under high doses of quetiapine and recovered in the course of the next months after quetiapine was stopped[43]. While temporary cessation of treatment can lead to severe psychotic exacerbation and nonengagement with cardiac specialists, more evidence is required for continued use of antipsychotics in patients with cardiac complications[42].

PATHOLOGICAL CHANGES OF ANTIPSYCHOTICS CARDIOTOXICITY

Chronic exposure to antipsychotics may directly damage cardiac muscles that lead to irreversible cardiac remodeling, pathologically diagnosed as myocarditis, dilated cardiomyopathy (DCM), and some other conditions, including ventricular hypertrophy, IHD, and pulmonary thromboembolism (PTE). In addition, emerging studies have reported that substantial fatal cases are negative for autopsy findings or with only mild pathological lesions, the causes of which are referred to as cardiac arrhythmia (summarized in Figure 2).

Myocarditis and DCM

Myocarditis is defined as inflammation of the myocardium. Clozapine is by far the

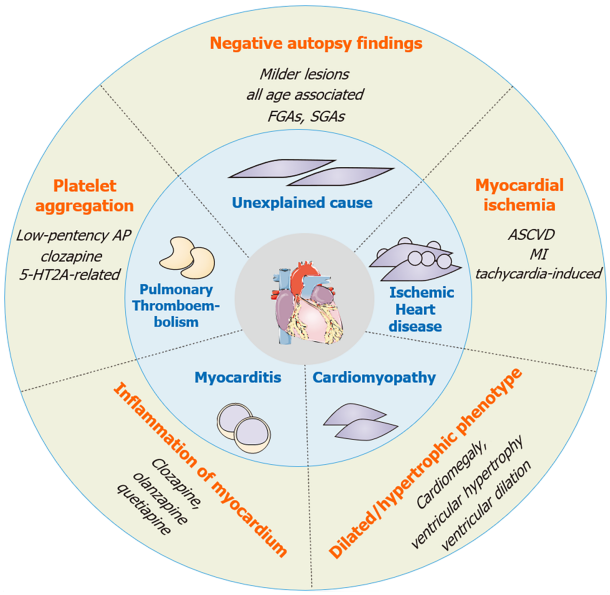


Figure 2 Summary of cardiac pathological changes in response to antipsychotic treatments. Typical characteristics of each pathological change are concisely listed in black text. SGA: Second-generation antipsychotic; FGA: First-generation antipsychotic; ASCVD: Atherosclerotic cardiovascular disease; MI: Myocardial infarction.

most commonly used antipsychotic that has been associated with myocarditis. The World Health Organization has suggested that clozapine, which caused over 200 cases of myocarditis and cardiomyopathy in 2001[44], has a closer association with myocarditis and cardiomyopathy than any other kind of antipsychotic drug[45]. According to statistics, clozapine-associated myocarditis has been estimated to increase from 1 in 10000 to 1 in 500 patients. Most of these cases occurred in the first 2 mo after clozapine therapy[46], while at the beginning of drug use, the incidence of clozapine-related myocarditis is between 0.03% and 0.19%[47]. Furthermore, the death rate caused by clozapine-induced acute myocarditis is approximately 25%[48]. An autopsy report also confirmed antipsychotic-induced myocarditis, which showed that in 24 sudden death cases, 11 (45.8%) died from myocarditis, and 7 (29.2%) were on clozapine medication[49].

The histopathological features in the case of clozapine-related myocarditis are myocytolysis and necrosis with florid infiltration, accompanied by lymphocytes, neutrophils, and prominent eosinophils[41]. If acute myocarditis is not recognized at the early stage, it may progress to DCM, a disease characterized by ventricular dilation and heart dysfunction. According to Kilian *et al*[41], the incidence of DCM in the general population was 0.75% to 1%, while that in clozapine-treated patients was approximately 5.15% (over a 5-fold increase compared with the general population). In an autopsy report, 6 (42.9%) in 14 cases died suddenly from DCM, which developed after chronic antipsychotic use[50].

The mechanism by which antipsychotics induce myocarditis or DCM remains unclear. Numerous hypotheses have been proposed, including immunoglobulin (Ig)E-mediated pathways, cytokine-driven responses, and oxidative stress-related hypercatecholaminergic states[51]. While IgE-mediated hypersensitivity used to be considered the main attributor, a recent study found that clozapine treatment caused an elevated plasma catecholaminergic state, and the blockade of β-adrenoceptors may be helpful in decreasing the occurrence and severity of clozapine-induced myocarditis, implicating a membrane receptor-involved mechanism[52]. We also reported that myocarditis is not always accompanied by aberrant eosinophils in experimental murine models[53], implying IgE-independent mechanisms underlying antipsychotic-induced cardiac muscle disorders.

Olanzapine- and quetiapine-induced myocarditis has also been sparsely reported due to their chemical structure similarity with clozapine. Quetiapine induced cardiomyopathy in a 37-year-old woman after high dosages[43]. From the spontaneous adverse drug reports database of the Danish Health and Medicines Authority, two fatal cases of eosinophilic myocarditis were associated with the use of olanzapine [54]. Another case report with 10-year olanzapine intake also suggested that the use of olanzapine may cause DCM since echocardiography shows decreased global biventricular function[55]. It has also been mentioned in another report that the

adverse drug reaction of psychotropic drugs (clozapine and olanzapine) is very likely to be related to DCM[56].

Ischemic heart diseases

It has been reported that most patients with schizophrenia do not die from suicide or during psychotic episodes but from IHD[57]. IHD has become the primary cause of death among schizophrenia patients[58] and tends to be sex biased. According to a statistical analysis, antipsychotics increased the prevalence of acute IHD by 32% among women but caused no significant changes among men[59]. The four antipsychotic drugs associated with high mortality of IHD were clozapine, quetiapine, olanzapine, and thioridazine, all of which share high affinity to the 5-HT2A receptor [60], and blockade of the 5-HT2A receptor might confer protection against IHD and buffer the deleterious metabolic effects of antipsychotics[61].

Among IHDs, myocardial infarction (MI) is a severe pathological alteration after the use of antipsychotic drugs[62]. It has been reported that antipsychotic users were 1.88-fold more likely to have MI[63], although this conclusion was challenged by a meta-analysis reporting no significant association with antipsychotic drugs[62]. The high incidence of MI might be attributed to atherosclerotic cardiovascular diseases (ASCVDs), which account for 67.3% of the natural deaths among schizophrenia patients in Maryland, USA[58]. ASCVD may manifest ischemic syndromes, including acute coronary syndromes, congestive heart failure, and sudden and nonsudden cardiac death[64]. The mechanism of ASCVD being common among schizophrenia patients is multifaceted, with the gut microbiome interrupted by antipsychotic use being recently introduced as a novel mechanism[65]. Interestingly, a study showed that haloperidol, a representative FGA, inhibited atherosclerosis in mice lacking LDL receptors by decreasing ABCA1-mediated cholesterol efflux from macrophages to apolipoprotein A1[66]. Another contributor to myocardial ischemia might be antipsychotic-induced tachycardia that increases myocardial oxygen demand and aggravates cardiac ischemia in schizophrenia patients[35].

Ventricular hypertrophy

In an autopsy-based study, two (14.3%) in 14 cases were found to have remarkable left ventricular hypertrophy, leading to the diagnosis of hypertrophic cardiomyopathy [50]. We also reported a case of sudden death from hypertrophic cardiomyopathy after over 20 years of chlorpromazine therapy[40]. Ventricular hypertrophy might be an adaptive response in the early stage of antipsychotic stimuli. When maladapted, the heart may progress to pathological hypertrophy, a condition that predisposes patients to sudden death.

Pulmonary thromboembolism

Antipsychotic drugs have also been reported to cause thrombotic complications such as lupus-like syndromes. Both typical and atypical antipsychotics can cause PTE[67]. Female sex and the use of antipsychotics were two risk factors for PTE, with odds ratios of 4.22 (95%CI: 1.82-9.78) and 10.49 (95%CI: 3.95-27.85), respectively[68]. Among 28 patients who died of PTE, eight (28.6%) used antipsychotics, and all were female [68]. High-dose and parenteral administration were also more likely to cause PTE. For oral administration, the odds ratio was 1.07 for the low dose ($P = 0.04$) and 1.40 for the high dose ($P < 0.001$). For parenteral administration, the odds ratio was 1.18 for the low dose ($P < 0.001$), while it was 1.43 for the high dose ($P < 0.001$)[69]. In particular, the use of low-potency antipsychotic drugs was associated with a higher risk of venous thromboembolism (risk ratio = 1.90, 95%CI: 1.04-3.47), a condition that predisposes patients to PTE[70]. Generally, chlorpromazine, thioridazine, and clozapine are common antipsychotics that cause PTE.

The development of PTE has been associated with increased platelet aggregation due to the strong affinity of these drugs for 5-HT2A receptors. According to statistics, atypical antipsychotic drugs have a more than 10-fold greater affinity for 5-HT2A receptors than for D2 receptors[68]. Antipsychotics may also block dopamine and then cause hyperprolactinemia, which is a significant risk factor for PTE in patients using antipsychotics. Of note, although aripiprazole and quetiapine act on 5-HT2A receptors, they did not increase the risk of PTE. Another report also showed no increase in platelet aggregation caused by haloperidol, olanzapine, and risperidone[71], although this finding contradicts sporadic case reports of olanzapine and risperidone-associated PTE[72]. These studies imply extra 5-HT2A receptor-independent mechanisms or potential between-study heterogeneity.

Sudden unexplained death

It is noteworthy that even after systemic autopsy and toxicological screening, some cases may have no definitive cause of death, the so-called "unexplained" autopsy-negative cases that are probably caused by cardiac arrhythmia. Many autopsy-based studies have documented unexplained cases among sudden deaths of schizophrenia, with rates ranging from 2.8%[58] to 52%[73]. A nationwide cohort study from Denmark found that SCDs in psychiatric patients were more often unexplained than those in nonpsychiatric patients (65% *vs* 40%, P = 0.02)[5]. The incidence of unexplained deaths tends to increase across years, as the deaths per 100000 patient-years dramatically increased from 7 (95%CI: 3.7-19.4) in 1984-1998 to 125 (95%CI: 88.9-175.1) in 2005-2009[73]. The unexplained cases were similar to the explained cases regarding demographic features, psychiatric diagnoses, and use of psychotropic classes (FGAs and SGAs). Dyslipidemia (P = 0.012), diabetes (P = 0.054), and comorbid dyslipidemia and diabetes (P = 0.006) were more common in the unexplained group [73].

In particular, there have been six autopsy-based reports that highlight unexplained deaths. The detailed forensic characteristics are documented in Table 1. Specifically, these unexplained cases were found at all ages, ranging from 2 to 86 years old. Male decedents were more common (57.8%). All decedents were overweight or worse, which conforms to the notion that dyslipidemia and diabetes were more common in unexplained deaths[73]. Approximately half of these unexplained deaths were negative for any autopsy findings. Before the introduction of SGAs, the FGAs chlorpromazine and haloperidol were common drugs, while after the introduction of SGAs, quetiapine, olanzapine, and clozapine were the primary drugs associated with unexplained deaths. Most of these cases were at a therapeutic dose, with the exception of the eight unexplained cases whose postmortem levels of antipsychotics were up to toxic concentrations[74].

MECHANISMS UNDERLYING ANTIPSYCHOTICS CARDIOTOXICITY

Subcellular organelles

Mitochondria: It has been reported that the antipsychotic drug clozapine undergoes bioactivation to a reactive nitronium ion by dehydrogenation in mitochondria; subsequently, this electrophilic intermediate is detoxified by conjugation with reduced glutathione[76]. The clozapine-glutathione conjugates are then eliminated in the bile of rats and mice over a 3-h period[77]. Thus, cardiac mitochondria may be a target for antipsychotic-associated adverse cardiac effects. Drug-induced functional and/or structural variations of cardiac mitochondria may result in myocarditis and cardiomyopathy by various approaches[78]. One possible mechanism of cardiac mitochondrial damage may involve antipsychotic bioactivation by cardiac tissue-specific microsomal CYPs and/or soluble oxidases/peroxidases, translocation of the resultant reactive metabolite to mitochondria, and alkylation of mitochondrial proteins[79], a mechanism similar to paracetamol-induced hepatoxicity[80]. Furthermore, the parent drug and/or its metabolite(s) may enter cardiac mitochondria to form nitronium ions, which localize within this organelle and consequently cause drug accumulation in the heart [79]. In addition, chronic dosing with haloperidol and some SGAs (*i.e.*, clozapine and risperidone) could result in loss of complex I, the electron transport chain component in mitochondria, to generate side effects[81,82] and negatively affect mitochondrial bioenergetics[81]. Proteomic profiling revealed that mitochondrial function and oxidative phosphorylation were significantly affected in risperidone- and olanzapine-treated mouse hearts, additional evidence supporting risperidone-altered cardiac mitochondrial oxygen consumption[83].

Lysosomes: Lysosomes contain over 30 acid hydrolases and are a significant acidic compartment to digest and phagocytose during antipsychotic metabolism[84]. Most antipsychotics are basic lipophilic compounds, the distribution of which is determined by cellular membrane phospholipid binding[85] or by lysosomal trapping[86]. For lysosomal trapping, basic lipophilic drugs permeate membranes and aggregate in lysosomes. The acidic interior of lysosomes then protonates the parent drugs or metabolites, preventing them from returning to the cytosol, an approach directly leading to detoxification of drugs[84]. Unfortunately, unlike the liver, lung, and kidney, the heart is a lysosome-deficient organ that exerts a very weak capacity to capture and protonate drugs[87]. This natural defect directly results in failure of drug protonation after entering cardiac cells and explains the exclusive cardiotoxicity of

Table 1 Six autopsy-based studies assessing demographic and forensic characteristics of sudden unexplained deaths after antipsychotic use

Category	Sweeting *et al* [7]	Ifteni *et al*[75]	Sun *et al*[58]	Ye *et al*[40]	Jusic and Lader[74]	Manu *et al*[73]
Publication year	2013	2014	2019	2018	1994	2011
Case region	Sydney, Australia	Brasov, Romania	MD, United States	Shanghai, China	London, United Kingdom	New York, United States
Reported case number	72/683	6/57	11/391	5/24	8 case reports	52/100
Age, yr (mean ± SD)	53 ± 14	55 ± 13	36 ± 17	57 ± 5	36 ± 14	50 ± 13
Males, *n* (%)	41 (56.9)	4 (66.7)	7 (63.6)	1 (20.0)	5 (62.5)	31 (59.6)
BMI (kg/m^2)	26.0 ± 7.1	26.0 ± 4.8	31.0 ± 7.2	NA	NA	NA
Autopsy finding[1], *n* (%)	NA					NA
Mild atherosclerosis		3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Chronic pericarditis		1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Myocardial dystrophy or fibrosis		1 (16.7)	2 (18.2)	0 (0.0)	1 (12.5)	
Ventricular dilation		0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)	
Cardiomegaly		0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)	
Conduction system abnormality		0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	
Lung edema, congestion		1 (16.7)	0 (0.0)	0 (0.0)	4 (50.0)	
None		0 (0.0)	5 (45.5)	3 (60.0)	4 (50.0)	
Postmortem toxicology[1], *n* (%)	NA	NA				
First-generation						4 (7.7)
Chlorpromazine			0 (0.0)	2 (40.0)	5 (62.5)	
Haloperidol			0 (0.0)	1 (25.0)	5 (62.5)	
Thioridazine			0 (0.0)	0 (0.0)	1 (12.5)	
Droperidol			0 (0.0)	0 (0.0)	2 (25.0)	
Promazine			0 (0.0)	0 (0.0)	1 (12.5)	
Trifluoperazine			0 (0.0)	0 (0.0)	1 (12.5)	
Pimozide			0 (0.0)	0 (0.0)	2 (25.0)	
Fluphenazine			0 (0.0)	0 (0.0)	2 (25.0)	
Second-generation						
Olanzapine			0 (0.0)	2 (40.0)	0 (0.0)	2 (3.8)
Quetiapine			4 (36.4)	1 (25.0)	0 (0.0)	11 (21.2)
Clozapine			2 (18.2)	1 (25.0)	0 (0.0)	5 (9.6)
Risperidone			0 (0.0)	0 (0.0)	0 (0.0)	4 (7.7)
Ziprasidone			0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Negative			5 (45.5)	0 (0.0)	0 (0.0)	0 (0.0)

[1]Some cases are presented with ≥ 2 autopsy findings or drugs, so the sum may exceed the total number of columns. BMI: Body mass index; NA: Not available.

antipsychotics. Moreover, polypharmacy is common among patients with mental disorders. When two or more basic lipophilic drugs are trapped by lysosomes, the pH increases more than when a single drug is trapped. Lysosomes are then oversaturated and diminish the drug intake capacity[84]. This is a phenomenon called synergistic

effect.

Molecular mechanisms

Ion channels: Cardiac action potentials are generated by transmembrane movements of ion species, flowing principally through specific channels. Antipsychotics can affect a variety of cardiac ion channels, especially the potassium channel (particularly the potassium rapid delayed rectifier channel, K_r), which is associated with QT interval prolongation and lethal cardiac arrhythmias such as TdP[88]. The K_r channel, also known as the hERG channel, is encoded by the human ether-a-go-go related gene (*hERG*). Almost all antipsychotics could modulate cardiac K_r channels. Risperidone and its active metabolite paliperidone inhibited the potassium current by interacting with the open and inactivated states of the I_{Kr} channel without affecting channel protein trafficking[89]. FGAs (chlorpromazine and thioridazine) and clozapine suppress the current of the K_r channel and consequently result in QT prolongation. Olanzapine, a first-line SGA in the clinic, blocked the K_r current in a concentration-dependent manner with a tail current decrease of 50% at 3.8 mmol/L olanzapine[90]. Of note, the 50% inhibition concentration (IC_{50}) of this iron channel has drug-based differences, ranging from 1 nmol/L (haloperidol)[91] to 6 μmol/L (olanzapine)[92]. This variation is not related to a class effect (FGAs *vs* SGAs) but seems to relate to the potency of antipsychotics to block hERG channels[93].

Genetic susceptibility, namely, mutations in the genes encoding potassium ion channel proteins (*i.e.*, *KCNH2*, *KCNQ1*, and *SCN5A*) is also directly associated with an increased risk of malignant arrhythmias[94]. In addition to the inherited *hERG* mutations that are associated with congenital long QT syndrome, suppression of native I_{Kr} by psychotropic therapy also predisposes individuals to polymorphic ventricular tachycardia of the TdP type[95]. Hence, genetic screening should be implemented in selected patients who have previous episodes of drug-induced arrhythmias.

Biological membrane receptors: As mentioned above, due to their lipophilic nature, antipsychotics might exert their cardiac effects by perturbing the physical properties of biological membranes[96]. The membrane-resided receptors may thus be involved.

Adrenoceptors: There are many antipsychotics that have a strong affinity for adrenoceptors. For example, the FGA droperidol competitively interacts with vascular α-adrenoceptors but has no effect on β-adrenoceptors[97]. The potency of binding to α1- and α2-adrenergic receptors varies among these medications, with a 532-fold range for α1 antagonism and a 400-fold range for α2 antagonism among atypical antipsychotics [98]. There are several lines of evidence for the involvement of adrenoceptors in antipsychotic cardiotoxicity. First, as the endogenous ligand of adrenoceptors, plasma noradrenaline levels significantly increased in patients upon clozapine maintenance treatment[99]. Similarly, in a rat model receiving multiple doses of the FGA haloperidol and SGAs (risperidone, clozapine, and olanzapine), the plasma catecholamine levels were found to be significantly elevated by all antipsychotics, although the elevation was drug- and dose-dependent[100]. Compared to other antipsychotics, intravenous injection of olanzapine and clozapine seemed to cause a more significant increase in plasma epinephrine. Second, a β-adrenergic blocking agent, propranolol, was found to significantly attenuate clozapine-induced myocarditis in a murine model[52], posing a direct linkage of adrenoceptors to antipsychotic cardiotoxicity.

Cannabinoid receptors: Given that β-adrenoceptor blockade produced only a partial reduction in clozapine-induced TNF-α levels[52], other receptors were later proposed to be functional. In our serial works, we found that clozapine[53] or quetiapine[101] treatments caused a decrease in cannabinoid receptor 1 (CB1R) while increasing CB2R expression within approximately 2 wk of treatment in mice. The ligands of these receptors were disrupted in a dose- and time-dependent manner. Furthermore, in cultured cardiomyocytes, the CB1 receptor was observed to translocate from the cytomembrane in intact cells to the cytoplasm/nuclei in SGA-treated cells, whereas the CB2 receptor went the opposite way in SGA-treated cells[53,101], suggesting a functional rivalry between the cannabinoid receptor subtypes[102]. Furthermore, both cannabinoid receptors regulated a new type of necrotic cell death[101], termed necroptosis, which explained the clinical association of antipsychotic use with inflammatory states. The opposite roles of cannabinoid receptors suggested that the treatment of antipsychotic cardiotoxicity might only be beneficial when based on single-receptor agonism or antagonism[102].

Other molecular mechanisms: Several pathways were also reported to be associated with clozapine-induced myocarditis. Clozapine, particularly at relatively high doses, has a clear cardiotoxic effect, as evidenced by increased myocardial oxidative stress, inflammatory cytokines, DNA damage, and apoptosis with attenuation of antioxidant defenses. The use of captopril, an angiotensin-converting enzyme inhibitor, significantly protected against the above clozapine-induced effects in rats[103]. In a rat model, olanzapine-induced cardiotoxicity was reported to be associated with increased acetyl-CoA carboxylase phosphorylation and tissue ATP levels and lower phosphorylation levels of Akt and its downstream product AS160[104]. These generally descriptive studies reinforced the mitochondria-involved mechanisms and implied that inflammatory cell death might be critically involved in antipsychotic cardiotoxicity. By integrating proteomic and transcriptomic approaches, we recently further found that representative SGAs share a similar cardiac pathological basis to cause cardiotoxicity, and spliceosome signaling represents a common intracellular mechanism underlying SGA-induced cardiotoxicity[105]. SGA-dysregulated spliceosome signaling was only partially rescued by pretreatment with an agonist of histamine 1 receptor (HRH1)[105], implying additional membrane receptor-involved mechanisms.

FUTURE PERSPECTIVES

Clinical monitoring

Many approaches have been recommended for the clinical monitoring of antipsychotic cardiotoxicity, including biomarker detection (*i.e.*, CRP, creatine kinase, and cardiac troponins), ECG monitoring, echocardiogram monitoring, and B-type natriuretic peptide (BNP) detection.

Creatine kinase has been found to be less useful than troponin to assess myocardial injury due to its low sensitivity (approximately 22%)[106]. Troponins appear to have a higher sensitivity of approximately 39% but can only be true-positive in the first month after disease onset. The specificity of troponin is approximate 89%[107]. The sensitivity of ECG monitoring is approximately 35% (equal to that of peripheral eosinophilia detection), while creatine kinase isoenzyme (CK-MB) only has a 5.7% sensitivity rate[107]. The test with the highest sensitivity is left-ventricle hypokinesis and/or reduced ejection fraction by echocardiogram, although only 48%[108]. A clinical study over the years 1994-2009 concluded that combining troponin (over twice the upper limit) and CRP (over 100 mg/L) had an estimated diagnostic sensitivity of 100% for symptomatic clozapine-induced myocarditis[109]. A recommendation was also proposed to regularly monitor CRP, troponins, and ECG at baseline and at weeks 1, 2, 3, and 4 to improve the early detection of clozapine-induced myocarditis[110].

The above approaches have been clinically practiced for decades and, however, are not exclusive for monitoring antipsychotic-induced cardiotoxicity. BNP is a 32-amino acid vasoactive peptide that is primarily secreted by the ventricular wall[111]. It acts as a key response to increased wall stress and a vital regulator in the homeostasis of water and salt excretion[112]. A clinical study has documented the potential of using an N-terminal fragment of BNP (NT-proBNP)[113] in combination with QTc measurement as a highly accurate marker for the early detection of acute antipsychotic drug-induced cardiotoxicity. Of note, these clinical studies are limited to a small number of patients. Multicenter studies with larger sample sizes are mandated to verify the association between NT-proBNP levels and acute cardiac toxicity.

In recent years, implantable cardioverter defibrillators (ICDs) have been considered the most effective treatment for patients at high risk of SCD[114]. Individual wrist-worn medical devices with the capability of monitoring several fatal biometrics, such as HR and BP, as well as ECG have also been recommended[115]. This high-tech wrist-worn device has multiple advantages over other biochemical tests due to better prediction and management of patients and the real-time notice of irregular heart rhythm and other warnings to users receiving antipsychotic therapy.

Therapeutic agents

Some studies have reached a consensus that the addition of β-blockers has been an effective clinical alternative for the treatment of clozapine-associated tachycardia[116]. Taking low doses of bisoprolol, for example, can be well tolerated and may offer symptomatic relief in patients who are aware of and suffer from tachycardia[117].

In addition, we have provided profound data that two subtypes of cannabinoid receptors (CB1R and CB2R) are critically involved in antipsychotic cardiotoxicity. Specific antagonists of CB1R or agonists of CB2R bring beneficial effects, including inflammation suppression and fibrosis remission in the heart[53,101]. Meanwhile, it would not profit from dual antagonists or agonists since dual binding might neutralize the effect of each other. Therapeutics should be mono-receptor based[53,101]. In particular, antagonists of CB1R have been marketed for weight loss, and CB2R agonists have also been associated with a welcome metabolic process[118]. Since metabolic and cardiovascular adverse effects are the major dilemma associated with antipsychotic drug use[119], the use of CB1R antagonists or CB2R agonists in combination with antipsychotics might be conceived to exert dual protection: One to inhibit drug cardiotoxicity and the other to ameliorate antipsychotic-induced weight gain. Of note, individual CB1R antagonists may cause additional psychiatric disorders due to brain penetrance and have been withdrawn from clinical use (*i.e.*, rimonabant [120]). Therefore, the development of peripherally restricted CB1R antagonists or CB2R agonists would provide dual protection against these clinical concerns without causing additional toxicity[121].

Third-generation antipsychotics

There are several new and emerging antipsychotic medications, termed TGAs, recently marketed or under clinical development for the treatment of several mental disorders [2]. Overall, TGAs display a good safety profile, with a well-demonstrated lower metabolic liability than SGAs. Furthermore, TGAs appear to specifically target negative symptomatology and improve cognitive domains[2].

Comparing the cardiac adverse effects of recently developed antipsychotics (brexpiprazole, cariprazine, lurasidone, pimavanserin, and roliperidone)[122], roliperidone showed the lowest incidence of cardiovascular effects and metabolic influences, such as hypotension, QTc prolongation, weight gain, and metabolic syndrome, which indicates a potential therapeutic method to offset the defects of SGAs. Further clinical trials are needed for safety and efficacy evaluation.

CONCLUSION

This review introduces the clinical manifestations and pathological lesions in antipsychotic cardiotoxicity. Although largely unknown, many mechanisms at the subcellular organelle level (mitochondria and lysosomes) and at the molecular level (membrane receptors and ion channels) have been independently reported. This merits future evaluation of the efficacy (sensitivity and specificity) of the recently developed monitoring approaches. To avoid drug discontinuation or withdrawal from the market, drug adjuvant therapy to alleviate both cardiotoxic and metabolic effects is preferentially favorable. TGAs, particularly those with favorable cardiac and metabolic outcomes, deserve clinical application. Larger cohort-based clinical evaluations are needed for the development of receptor-targeted adjuvant drugs.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 754-773

DOI: 10.5498/wjp.v11.i10.754

ISSN 2220-3206 (online)

REVIEW

Therapeutic role of yoga in neuropsychological disorders

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Author contributions: Nourollahimoghadam E, Gorji A, and Khaleghi Ghadiri M contributed to the conception and design of the study; Nourollahimoghadam E and Gorji S contributed to searching and accumulation of the data and writing and drafting of the preliminary manuscript; Gorji A and Khaleghi Ghadiri M contributed to critical revision of the final draft of the manuscript; All authors approved the final version of the manuscript.

Conflict-of-interest statement: There is no conflict of interest.

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Abstract

Yoga is considered a widely-used approach for health conservation and can be adopted as a treatment modality for a plethora of medical conditions, including neurological and psychological disorders. Hence, we reviewed relevant articles entailing various neurological and psychological disorders and gathered data on how yoga exerts positive impacts on patients with a diverse range of disorders, including its modulatory effects on brain bioelectrical activities, neurotransmitters, and synaptic plasticity. The role of yoga practice as an element of the treatment of several neuropsychological diseases was evaluated based on these findings.

Key Words: Complementary medicine, depression; Bipolar disorder; Schizophrenia; Anxiety; Migraine; Parkinson's disease; Alzheimer's disease; Epilepsy; Multiple sclerosis

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Core Tip: A multitude of beneficial effects of yoga practice and the underlying mechanisms of action have been reported and point out its role as an influential element in the integrative therapy of various neuropsychological disorders. In the planning of further investigations, studies should be designed to achieve more accuracy and precision in the heterogeneous field of yoga practices and potential fields of application.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Germany

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 24, 2021
Peer-review started: February 24, 2021
First decision: June 24, 2021
Revised: June 28, 2021
Accepted: August 2, 2021
Article in press: August 2, 2021
Published online: October 19, 2021

P-Reviewer: Byeon H, Stoyanov D
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Wang LYT

Citation: Nourollahimoghadam E, Gorji S, Gorji A, Khaleghi Ghadiri M. Therapeutic role of yoga in neuropsychological disorders. *World J Psychiatr* 2021; 11(10): 754-773
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/754.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.754

INTRODUCTION

Several neurological disorders affect mental health and lead to various degrees of impairment in cognitive functions. The use of complementary and alternative medicine, practices that improve the mind's capacity and body function, amongst patients with neuropsychological disorders is increasing worldwide[1,2]. Biofeedback, homeopathy, acupuncture, meditation, and yoga are among the different categories of these interventions[3]. Yoga is a form of mind-body technique that involves and contributes to both mind and body[4] and has been used as a therapeutic intervention in various neurological and psychological disorders[5]. The word "Yoga" is derived from the Sanskrit origin "yuj" meaning "yoke" or "union," and it is assumed that yoga describes the union between mind and body[5]. As an ancient Indian non-religious mind-body method[2,6], yoga is considered a philosophical and spiritual discipline that alleviates suffering and promotes human health[4]. Yoga has been practiced in Eastern cultures as a spiritual healing method for over 4000 years. The "Yoga sutra," a 2000-year-old guidebook, is the earliest known document of yoga that provides the framework of all branches of yoga. This book conceptualized yoga as eight limbs, which were designed to be practiced in sequence[7-9]. There are several styles of yoga, and no one is superior to another (Table 1).

A rapid increase of interest in yoga in Western countries occurred in the first decades of the 19th century, which has continued to this day. The National Health Interview Survey has reported that the number of people in the United States who practice yoga has increased dramatically among all age groups between 2002 to 2012[9,10]. Yoga practice can be a treatment for a variety of disorders as well as physical exercise[9]. This leads to an increase in investigations focusing on the mechanism of action and effect of yoga intervention on various mental and physical conditions[9-11]. Yoga interventions can maintain brain health through various mechanisms, such as the improvement of cerebral oxygenation[12], enhancement of neurotrophic and angiogenic factors (such as angiogenin)[13], balancing the excitatory/inhibitory neurotransmitter equilibrium[14], modulation of immune responses[15], and prevention of oxidative stress[16]. In the present review, we first show data that point out the effect of yoga on the brain under physiological conditions. Then, we review the effect and potential mechanism of action of yoga in the treatment of neurological and psychological disorders.

EFFECT OF YOGA ON THE BRAIN

Yoga is a movement-based embodied contemplative activity that can lead to a variety of neurobiological alterations in different brain regions. Yoga exerts a regulatory effect on brain synaptic plasticity and promotes cognitive tasks, particularly working memory[17,18]. Furthermore, yoga increases inter-hemispheric coherence and symmetry and improves neurocognitive functions[19]. Yoga may also exert pronounced anatomical changes in different brain regions, especially in the limbic system[20].

Effect of yoga on brain neurotransmitters

γ-aminobutyric acid (GABA) is considered the main inhibitory neurotransmitter responsible for the regulation of cortical excitability and neural plasticity[21,22]. Multiple lines of evidence suggest that yoga promotes cortical GABAergic inhibitory tone and modulates downstream brain regions[14,23]. A 12 wk yoga practice markedly enhanced the thalamic GABA values, accompanied by improved mood and reduced anxiety[24]. Higher thalamic GABA levels could be the result of enhanced (regional) cerebral blood flow in the prefrontal cortex of yoga practitioners[25], which can lead to the activation of the reticular nucleus of the thalamus and higher GABA production [26,27]. A magnetic resonance spectroscopy study has shown that yoga practitioners exhibited greater brain GABA values after a 60 min session of yoga training compared

Table 1 Different types of yoga interventions

Type of yoga	Description
Ashtanga	Six series of postures during breathing exercises
Bikram	Twenty-six poses and a sequence of two breathing exercises that take place in heated rooms with high humidity
Hatha	Basic postures and poses with breath regulation and meditation
Iyengar	Focuses on the precise structural alignment of the body
Jivamukti	Physically intense challenging postures with meditation
Kripalu	Breathing exercises at the beginning, gentle stretches, and series of poses before final relaxation
Kundalini	Chanting at the beginning and meditation aiming to release energy
Sivananda	Based on a 5-point approach, including proper breathing, diet, relaxation, exercise, and positive thinking
Vini	Based on in-depth training aiming to be an expert on anatomy and yoga therapy
Prenatal	A type of yoga helping mothers with physical training and meditation
Yin	Focuses on releasing tension through different joints

to controls[28]. In addition to GABA, an enhancement of dopamine has been observed in the ventral striatum of subjects who practice yoga[25,29,30]. It has been suggested that yoga could cause a rise in serotonin. Several investigations performed on participants after their meditation sessions have shown an elevation of the serotonin metabolite levels in urine[25,31]. Moreover, a regular yoga practice may cause a reduction in norepinephrine values. Patients with heart failure who practiced weekly yoga displayed lower levels of norepinephrine in blood samples[30,32] (Figure 1).

Effect of yoga on the bioelectrical activities of the brain

Yoga practices regulate electroencephalogram (EEG) signals through switching off non-relevant neural circuits for the preservation of focused attention and blockade of inappropriate signals[33]. Studies on the effects of yoga on brain waves revealed that breathing, meditation, and posture-based yoga practice increase overall brain activity [19], particularly in the amygdala and the frontal cortex. Alpha brain waves predominate during active attention and thinking as well as in some meditative conditions and correlate with basic cognitive processes[34]. Alpha waves could reflect the physiological and pathological changes of the relevant neural network activity during conscious perception and working memory[35]. Investigations on brain waves in meditators concluded that meditation leads to the alterations in anterior cingulate and dorsolateral prefrontal cortices and the enhancement of alpha wave activity[36]. Beta brain waves are dominant during wakefulness with open eyes, which could be affected by stressful conditions[37,38]. An enhancement of EEG beta wave activity has also been observed after yoga meditation practices[39]. Beta wave activity is present throughout the motor cortex during isotonic contractions and slow movements and is related to gains in academic performance and high arithmetic calculation ability[19, 40]. Theta waves assist with alertness and the ability to process information quickly [36]. The occurrence of the higher theta wave activities is associated with lower levels of anxiety[36,41]. An increase in theta wave activity has been reported during meditation[30,36]. Longer duration of meditation is associated with higher theta and alpha wave activities[30,33,36].

Effect of yoga on brain structure and neural connectivity

Yoga intervention seems to be associated with brain structural alterations, particularly in the frontal cortex, amygdala, hippocampus, insula, and anterior cingulate cortex [42]. An investigation on regional differences in grey matter volume associated with the practice of yoga has shown a greater grey matter volume in different areas of the dominant hemisphere, including the ventromedial orbitofrontal, ventrolateral prefrontal, and inferior temporal and parietal cortices as well as the left insula in skilled practitioners of yoga[43]. Furthermore, elderly yoga practitioners with several years of yoga experience have shown greater neocortical thickness in the left prefrontal complex cluster, which includes part of the lateral middle frontal gyrus, dorsal superior frontal gyrus, and anterior superior frontal gyrus compared to healthy non-practitioners[44]. A magnetic resonance imaging study revealed the greater volume of gray matter in the left hippocampus in skilled yoga practitioners with at least 3 years

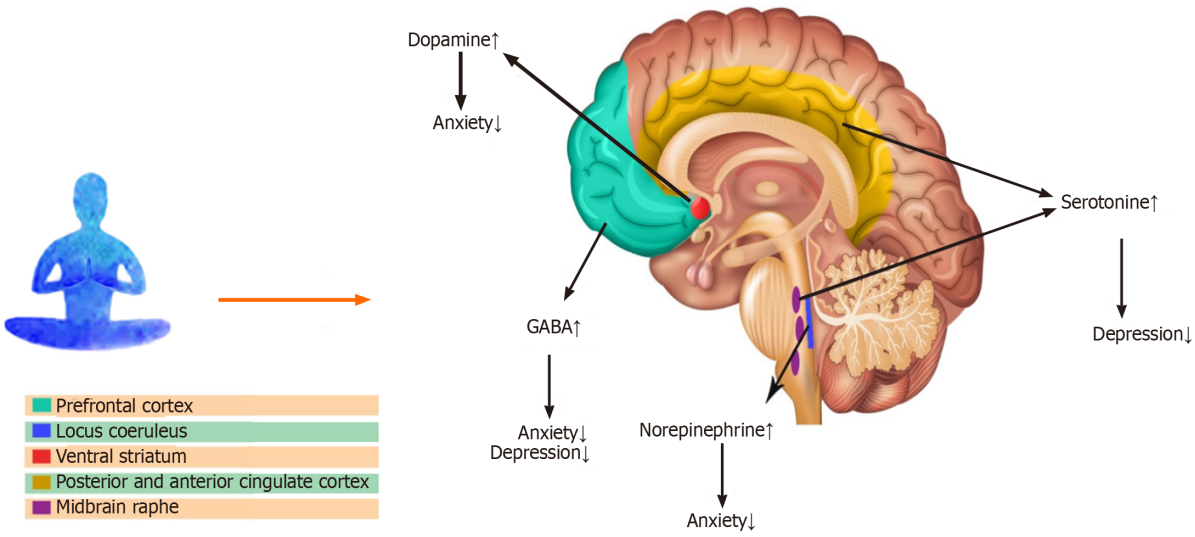


Figure 1 The effect of yoga intervention on various neurotransmitters in different brain regions. GABA: γ-aminobutyric acid.

of experience compared to the sex- and age-matched control subjects[18]. A population-based study on 3742 subjects revealed a lower right amygdala volume and a lower left hippocampus volume in those who participate in meditation and yoga practices[45] (Figure 2).

THE CLINICAL EFFECT OF YOGA

The clinical role of yoga on neurological disorders

Yoga and headaches: Several studies have suggested the beneficial effects of yoga in reducing the frequency and intensity of various forms of headaches, particularly migraine and tension headaches[46]. Yoga has been suggested as a potential complementary therapeutic intervention for headaches[47]. A meta-analysis on yoga for tension-type headaches and migraine has shown preliminary evidence of a short-term beneficial effect of yoga on tension-type headaches. This study revealed a significant improvement in the frequency, duration, and intensity of pain in patients with tension-type headaches[48]. A randomized controlled trial evaluating the beneficial effects of yoga on 114 patients with migraines has shown a significantly greater improvement in various migraine measures, including headache frequency, intensity, and use of rescue medications[49]. Another randomized controlled study with 19 subjects suffering from episodic migraine has shown a reduction in headache intensity, duration, depression, and anxiety as well as an improvement of self-efficacy, migraine-related disability, and quality of life from baseline to initial follow-up[50]. A significant improvement of self-perceived pain frequency, pain intensity and duration, and psychological status as well as a reduction in medication consumption was observed in 31 patients with chronic migraine[51]. Furthermore, a significant decrease in headache frequency, medication intake, and stress perception has been reported in 20 patients with migraine or tension headaches[52]. Yoga has been suggested as a potentially effective approach to reducing headaches associated with menopause[53].

Multiple investigations have explored the mechanisms of action of yoga on headaches. Migraine is a neurovascular disorder with significant upregulation of endothelial adhesion molecules[2,54]. It has been suggested that yoga intervention alleviates pain primarily *via* modulation of the pain perception system, including the anterior cingulate cortex, insula, sensory cortex, and thalamus[55]. A study on 42 women with migraines evaluated the effect of yoga on endothelial dysfunction in migraine patients. A 12 wk yoga training program increased delivering O_2 to the body and reduced peripheral vascular resistance with a significant reduction in plasma values of vascular cell adhesion molecule, which suggests an improvement of vascular function in patients with migraine[8,51,56,57]. The amplitude of the contingent negative variation, an ultra-slow neocortical event-related potential, is significantly greater in patients with migraine compared to healthy controls, which indicates higher cortical excitability[58]. Subjects with migraines, who practice meditation, including

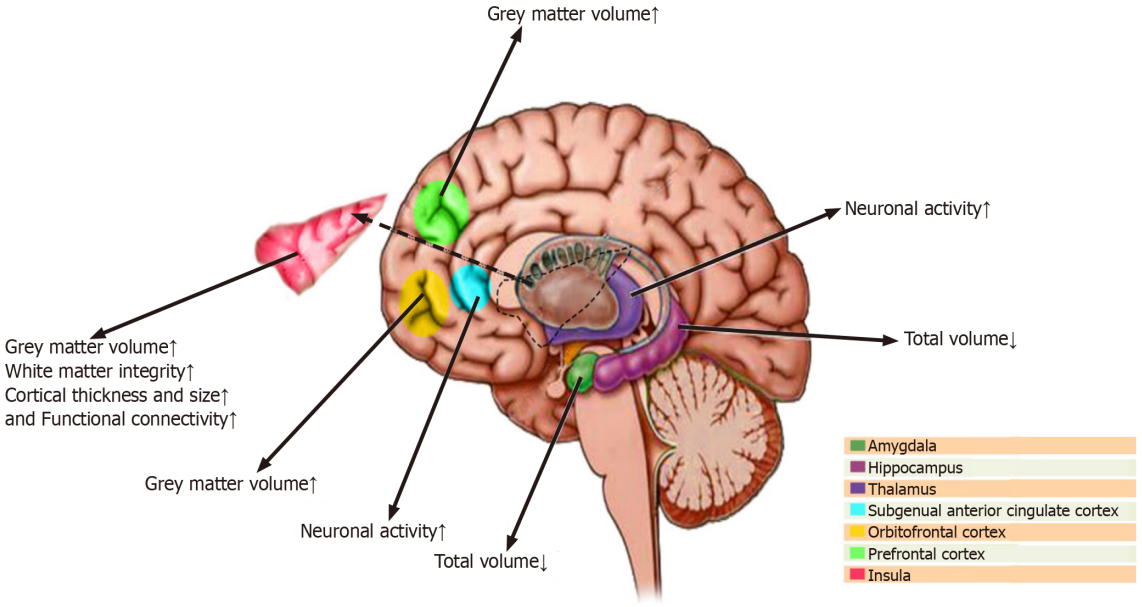


Figure 2 The effect of yoga practice on the functional activities of various brain regions.

yoga, have shown significantly lower amplitude of contingent negative variation[59].

Yoga and Alzheimer's disease: Alzheimer's disease (AD) is characterized by neuronal loss, mostly in the neocortex and the hippocampus[2,60], and is associated with memory and cognitive impairments and neuropsychiatric dysfunctions[2,60]. It has been suggested that yoga exerts a beneficial impact on overall brain health in healthy elderly subjects, older people with mild cognitive dysfunction, and subjects with dementia[61]. Yoga practice promotes cognitive function, affective interaction, and physical abilities of the healthy elderly population[62] and exerts a positive impact on total brain volume, neocortical grey matter thickness, and functional connectivity between different brain regions in subjects with mild cognitive dysfunction[63]. Using magnetic resonance imaging volumetric analysis, a trend toward decreased hippocampal volume atrophy has been observed after an 8 wk of yoga practice in patients with mild cognitive dysfunction[64]. A randomized neuroimaging study with 14 subjects has shown that yoga and mindfulness meditation may decrease hippocampal atrophy and promote functional connectivity between different brain regions, including the posterior cingulate cortex, the medial prefrontal cortex, and the hippocampus in adults susceptible to dementia[64]. Furthermore, it has been shown that mind-body interventions, such as yoga, can restore cognition in persons with mild cognitive impairment and delay the onset of AD[65,66]. Elderly subjects suffering from mild to moderate dementia have exhibited an improvement of behavioral impairments after a 12 wk yoga training program[67]. Metabolic enhancement for neurodegeneration, a novel therapeutic approach for AD, has merged yoga and meditation into other treatments of early AD pathology and achieved sustained cognitive improvement in 90% of patients[68]. Yoga may enhance blood flow to areas of the brain that modulate memory functions, reduce neuronal injury, promote the symptoms of early dementia, and delay the onset of AD[69]. Yoga can also improve the physical disability of patients with AD, such as walking, gait speed, and balance [70].

Although the mechanism of yoga action on AD needs to be elucidated, some possible mechanisms have been suggested. The serum values of several neurotrophic factors, such as brain-derived neurotrophic factor, increase after yoga practice in healthy individuals[71]. This may also occur in patients with mild to moderate AD and exerts a neuroprotective effect on the neurodegenerative process of AD[61]. The long-term practice of yoga also increases the serum value of serotonin[72]. The neuroprotective effects of yoga may be due to the enhancement of serotonin. Serotonin significantly destabilizes Aβ fibrils and protects neuron Aβ-induced cell injury and death[73]. The serum levels of melatonin significantly increased after a 3 mo period of yogic practices[74]. Melatonin reduces the Aβ level[75] and promotes microvessel abnormalities in the neocortex and the hippocampus[76] in experimental AD models.

Yoga and epilepsy: The goal of therapeutic approaches for epilepsy, a common neurological disorder characterized by abnormal electrical brain activity[77], is to eliminate or decrease the number and duration of seizures and improve the quality of life[2,78]. Several studies suggest that yogic practices can ameliorate seizures in patients with different types of epilepsy. An investigation on the effects of yoga intervention on seizures and EEG of 32 patients suffering from idiopathic epilepsy has revealed 62% and 83% reduction of seizure frequency 3 and 6 mo after the intervention, respectively. Furthermore, this study has shown a significant shift of EEG frequency from 0-8 Hz toward 8-20 Hz[79]. Another randomized controlled trial conducted on 20 children aged 8-12 years with epilepsy has suggested that a 6 mo yoga intervention as an additional therapy in children with epilepsy may lead to seizure freedom and a significant improvement of epileptiform EEG signals[80]. The evaluation of the effect of yoga on clinical outcomes of 300 patients with epilepsy has suggested that yoga is a helpful approach for patients to manage their disease[71]. Contrary to these reports, a clinical study reported no significant differences between the frequency of seizures between the yoga and control groups. Nonetheless, the yoga group showed significant improvements in their quality of life[81]. An analysis of the data of two clinical trials that evaluated the effect of yoga on 50 epileptic patients suggests a possible beneficial effect of yoga in the control of seizures[82].

Yoga and multiple sclerosis: Several clinical trials investigated the potential beneficial effects of yoga therapy in patients with multiple sclerosis (MS), an autoimmune neuroinflammatory demyelinating disorder of the central nervous system[83]. A study tested the effects of a 6 mo yoga intervention on the improvement of different aspects of physical as well as psychosocial conditions in 44 patients with MS and 17 healthy relatives. This investigation has shown significant improvements in the quality of life, walking speed, fatigue, and depression values. However, yoga did not promote the pain, balance, and physical status of these patients[84]. A pilot study on 12 patients suffering from MS has suggested that various yoga trainings for 6 mo may lead to a significant improvement in postural balance and daily physical activities[85].

Another clinical study on 24 participants diagnosed with mild to moderate MS, which underwent an intensive yoga practice for more than 4 mo, has shown marked improvements in the peak expiratory flow rate, physical conditions, mental health, and quality of life of patients with MS[86]. A study conducted on 60 female patients with MS revealed that yoga training significantly improved physical abilities and sexual satisfaction[87]. Yogic training and relaxation have also been suggested for the improvement of neurogenic bladder dysfunction in patients with MS[88].

A qualitative case investigation on a woman with MS suggested that individualized yoga intervention for 6 mo could be beneficial for the improvement of muscle tone and strength as well as self-confidence and stamina[89]. A significant improvement in balance, gait, fatigue, walking speed, and step length has been reported in 18 patients with relapsing-remitting MS after a 12-wk yoga training[90]. Yoga intervention has also exerted a beneficial role on improvements of postural balance and reduction of the influence of postural balance impairment during daily activities in patients diagnosed with MS after yoga practice for 6 mo[85]. A meta-analysis of 10 randomized controlled trials with overall 693 patients with MS who trained with different forms of yoga has revealed a significant improvement of fatigue but no effects on the overall quality of life, sexual function, and psychosocial condition[91].

Yoga and Parkinson's disease: The potential beneficial therapeutic effects of a yoga intervention for Parkinson's disease (PD), a chronic and debilitating neurodegenerative disorder, have been investigated. Yoga exerts a range of beneficial effects on different symptoms of PD[92]. A question-based survey on 272 patients with PD has shown that the majority of patients found yoga and meditation helpful for the alleviation of both motor and non-motor (fatigue, sleep difficulties, pain) symptoms [93]. A randomized clinical study on 126 patients with mild to moderate PD who underwent weekly yoga training for 8 consecutive weeks has shown a significant alleviation of psychological symptoms, improvement of the quality of life, and reduction of motor symptoms[94]. Yoga exercises can improve flexibility and balance, decrease muscle rigidity, increase the range of motion, and promote muscle strength in patients with PD[95]. Yoga intervention effectively improves balance and proprioceptive acuity in 33 patients with mild to moderate PD[96]. It has been suggested that incorporating yoga and occupational therapy may promote balance and decrease falls in patients with PD[97]. Yoga training decreases the back pain associated with a lower postural instability, which may reduce falls in patients with PD[98]. Furthermore, yoga as adjunctive therapy in patients with PD has been suggested as an effective treatment

for the reduction of psychological complications, particularly anxiety and depression [99-101].

Yoga and neuropathy: Peripheral neuropathy is a common neurological condition due to physical nerve injury, diabetes mellitus, autoimmune disorders, malignancy, kidney failure, nutritional deficiencies, systemic disorders, and idiopathic neuropathies, which can implicate the motor, sensory, and/or autonomous peripheral nerves[102, 103]. Several lines of evidence suggest that yoga may alleviate symptoms of various neuropathies[104,105].

Several reports suggest the beneficial effects of yoga practices in patients with neuropathy. Yoga practices were shown to improve numbness and weakness in lower extremities after a stretch or compression injury of the gluteal nerves[106], alleviate chronic pain due to diabetic neuropathy[107], and promote sensory functions and muscle movement in subjects with diabetic peripheral neuropathy[108]. However, it should be noted that some reports indicate yoga-induced nerve injury and neuropathy [109-111], particularly in patients who take sedative medications, people with benign hypermobility of their connective tissue, and the elderly[110,112,113]. Furthermore, yoga may ease compression and decrease nerve compression in carpal tunnel syndrome, which could lead to the improvement of numbness after a few weeks of practice[114,115]. Yoga mediation therapy improved the nerve conduction velocity, which was associated with glycemic control, in patients with diabetic neuropathy[116, 117]. A reduction of the impact of chemotherapy-induced peripheral neuropathy symptoms on the lives of patients with breast cancer as well as on the pain intensity after yoga intervention has been reported[118,119].

The clinical role of yoga in psychological disorders

Yoga, stress, and anxiety: Stress and anxiety are increasing in incidence worldwide. Approximately 34% of the general population is affected by an anxiety disorder during their lifetime[120]. Several investigations were performed on the feasibility and potential efficacy of different forms of yoga on anxiety- and stress-induced symptoms in both children and adults. It has been suggested that yoga may promote mental and physical strength, increase stress resilience, and reduce anxiety[121]. Although some studies do not show any effect[122,123], most investigations indicate that yoga can be effective in the alleviation of anxiety in the form of monotherapy or adjunctive therapy [124-127]. Functional magnetic resonance imaging evaluation revealed that yoga interventions modulate the activity of various brain areas that are crucial to emotion regulation, such as the superior parietal lobule and supramarginal gyrus, and lead to a diminished sympathetic response to stressful emotional stimulations[128]. Training of mindfulness- and yoga-based programs has shown a significant reduction of anxiety symptoms, which was associated with a marked decrease of structural connectivity of the right amygdala[129]. Furthermore, it has been suggested that yoga intervention modulates stress-induced autonomic regulatory reflex and inhibits the production of adrenocorticotropic hormone from the anterior pituitary gland[130], resulting in decreased production of cortisol from the adrenal gland[131].

A meta-analysis revealed that more yoga exercises were accompanied by greater benefits, particularly when subjects were suffering from higher values of anxiety at the early stages[132]. Another meta-analysis of eight trials with 319 adults diagnosed with anxiety disorders who underwent yoga training indicates that yoga could be a safe and effective intervention to reduce the intensity of anxiety[133]. Rhythmic yoga meditative interventions resulted in a reduction of stress associated with a higher plasma dopamine level together in 67 healthy subjects who regularly engaged in mind-body training[134]. Enhancement of dopamine values following yoga practice leads to a suppression of corticostriatal glutamatergic transmission and regulation of conscious states[29]. Yoga interventions have been suggested to enhance vigilance, improve sleep, and reduce anxiety in healthy security personnel[135].

Yoga-based exercises in schools have been suggested to reduce stress and challenging behavioral and cognitive responses to stress, promote physical ability, and strengthen cognitive performance among students[136,137]. Yoga interventions for a period of 8 wk have shown a significant impact on reducing anxiety in school-age children[138]. Using a yoga-based relaxation method (mind-sound resonance technique) alleviated state anxiety and mind wandering and promoted state mindfulness and performance in school children[139]. High-frequency yoga breathing training promotes attention and reduces anxiety in students aged 11-12 years[140]. Furthermore, evaluation of the effect of yoga intervention on stress perception and anxiety levels in college students has shown a significant reduction in anxiety and

stress scores associated with a marked enhancement of total mindfulness[141]. Yoga can also help adolescents hospitalized in an acute care psychiatric ward to lessen their emotional distress[142]. Yoga exerts a bifacial effect on the reduction of anxiety and improvement of self-esteem in orphanage residents[143].

Practicing yoga in patients suffering from post-traumatic stress disorder for at least 4 wk resulted in a significant reduction of cortisol values[144]. Yoga practices significantly reduce stress and anxiety in subjects living with human immunodeficiency virus[145], people with cancer[146], such as survivors of lung cancer[147] and patients with breast cancer[148], patients with systemic disease, like rheumatoid arthritis[149,150], and patients with neurologic disorders, such as PD[100]. Yoga exercises have also been suggested as a promising stress-relieving approach in pregnant women[151,152], in women receiving treatment for infertility[153], and in women who are trying to quit smoking[154,155].

Yoga and depression: Depression is the most common psychiatric disorder that affects 25% of women and 12% of men during their lifetime[156-159]. This disorder is commonly treated by antidepressants and psychotherapy[156,160]. Yoga interventions have been suggested as effective adjuvant therapy[161,162] as well as monotherapy [163] for depression.

A narrative review on the efficacy of yoga and mindfulness as an adjuvant treatment in severe mental illnesses including major depressive disorder (MDD) indicated that both yoga and mindfulness have significant and beneficial effects on reducing the severity of depressive symptoms[164]. Yoga practices in combination with the application of conventional antidepressants significantly improved depression symptoms and reduced the remission rate in patients with MDD compared to control patients[165]. A significant decrease in self-reported symptoms of depression after practicing yoga has been observed in individuals aged 18-29 with mild levels of depression[166]. A meta-analysis has shown a more significant reduction in depression compared to psychoeducation[167].

In addition to the improvement of depression, yoga interventions promote mental health and quality of life and interrupt negative thinking in patients with depression [168,169]. A meta-analysis of 10 studies has shown that yoga practices have a statistically significant effect as an adjunct treatment in patients with MDD[162]. In an investigation of hospitalized patients with severe MDD, the effect of yoga intervention was equivalent to treatment with a tricyclic antidepressant[170]. It has been suggested that yoga modulates cortical inhibition *via* the regulation of the GABAergic system and exerts beneficial effects in MDD[171]. Furthermore, increased GABA-mediated neurotransmitter activity induced by transcranial magnetic stimulation, and multiple yoga therapy sessions was associated with a significant improvement of depression symptoms in patients with MDD[172]. Enhancement of thalamic GABA values has also been suggested as a potential mechanism for the improvement of mood in patients with MDD[173]. Enhancement of serum neurotrophic factors, such as brain-derived neurotrophic factor, in patients with MDD who practiced yoga, pointed to the possible role of increased neuroplasticity in the improvement of depression symptoms [174]. Yoga practices in post-menopausal women resulted in reduced values of follicle-stimulating hormone and luteinizing hormone, which was associated with decreased stress levels and depression symptoms as well as improved quality of life[175]. Yoga practices in association with coherent breathing intervention have been shown to resolve suicidal ideation in patients with MDD[9,176].

Yoga and bipolar affective disorder: Bipolar affective disorder (BD) is a chronic illness with recurrent episodes of manic or depressive symptoms[177,178]. Although most patients with BD are free of symptoms during remission, many of them continue to experience mild symptoms and suffer from functional behavior impairments[177,179]. Studies on the role of yoga in the treatment of BD are scarce. However, some studies have recommended yoga as a specific self-management strategy for BD[5,180]. Patients with BD have shown a significant alleviation of depression and anxiety symptoms, reduction in difficulties with emotion regulation, and improvement of mindfulness skills during the remission phase following several weeks of yoga practices[181]. Yoga interventions have been suggested to decrease negative emotions in patients with BD [182]. Yoga has also been suggested as an adjuvant therapy that improves residual depression symptoms[183] as well as manic symptom severity[184] of patients with BD. An extensive multicenter, randomized controlled study on 160 adults with BD has shown that mindfulness-based cognitive therapy, including yoga practices, improves the severity of manic symptoms and anxiety, promotes mental health and overall functioning, and reduces relapse rates[185].

Yoga and schizophrenia: Schizophrenia (SZ) is a severe mental disorder, which often exhibits itself by positive symptoms, including hallucinatory experiences and delusional beliefs and negative symptoms, such as lack of motivation and social contacts as well as the absence of spontaneous speech and affective flattening[186-188]. A growing body of evidence suggests that yoga training as an add-on therapy could improve both the negative and positive symptoms and promote cognitive functions and emotional recognition of SZ[189-194].

The analysis of yoga intervention effects on the mood of 113 patients with psychosis has revealed significant improvements in tension-anxiety, depression, anger, fatigue, and confusion[195]. Another study on 66 antipsychotic-stabilized patients with SZ has revealed a significant improvement in positive and negative symptoms, socio-occupational functioning, and performance following yoga training[190]. A meta-analysis of 13 investigations with 1159 patients revealed the importance of the frequency of yoga interventions with an improvement of positive symptoms as well as the duration of each session with the alleviation of negative symptoms in patients with SZ[196]. Yoga practices in the patients with SZ who were taking antipsychotic medications and were in a stable condition significantly decreased drug-induced parkinsonian symptoms and improved executive functions and negative symptoms[192]. Long-term yoga intervention in patients with SZ resulted in greater social and occupational functioning and promoted the quality of life[197]. Yoga training in patients with SZ resulted in an improvement of negative and positive symptoms associated with a reduction of paranoid beliefs and promoting quality of life[198]. Yoga as an add-on treatment has shown a greater improvement of the negative symptoms of SZ in comparison to physical exercise therapy[197]. Furthermore, yoga therapy led to a significant reduction in burden scores and an improvement in the quality of life among patients with psychosis[199]. Yoga intervention in patients with SZ significantly improved cognitive dysfunction, presumably through the correction of autonomic dysfunction [200,201].

It has been suggested that yoga may improve SZ symptoms by strengthening the synaptic network of the lateral and medial prefrontal areas and augmentation of the premotor and parietal mirror neuron circuitry[202]. Oxytocin values increased significantly following yoga practice[203]; an effect that has been suggested to play a potential role in the improvement of social cognition after yoga intervention in patients with SZ[204]. Yoga practice in patients with SZ was also associated with a significant decrease in blood cortisol levels, suggesting a beneficial effect of yoga in the reduction of sociophysical stress of patients[204].

Yoga and other psychological disorders: Several other studies indicate the potential beneficial effects of yoga practices on other psychological disorders and syndromes, such as obsessive-compulsive disorder (OCD), burnout, somatoform disorders, and hypochondriasis[205]. The treatment of OCD with yoga together with the pharmacological interventions improved the obsessive thoughts and compulsive behavior of patients with OCD[206,207]. Furthermore, several clinical trials have suggested the promise of yoga intervention as an adjunct therapy for patients with OCD, who were unresponsive to conventional treatments[208,209]. Moreover, yoga training enhanced general satisfaction, improved work exhaustion, and led to greater work engagement and empathy among teachers[210], nurses[211], hospice professionals[212], and physicians[213,214], who were suffering from job burnout. Yoga can promote the psychological and physical well-being of subjects with burnout, particularly when combining it with other activities, such as art and music-therapy[215,216]. Furthermore, yoga-based interventions have been recommended as an effective therapeutic approach in somatoform disorders[217]. A 6 mo trial of yoga practices led to a significant improvement of somatoform symptoms, such as gastrointestinal, cardiovascular, and urogenital symptoms, in women with the menstrual disorder [218]. Several studies have revealed the beneficial effects of yoga interventions on the psychological health of the population during the global pandemic of coronavirus disease 2019[219].

ADVERSE EFFECTS OF YOGA

While yoga practice may exert various physical and psychological health benefits, there are some reports on its adverse effects. Intensive yoga training may lead to altered perceptions and beliefs in possessing supernatural powers. However, these psychological alterations can be interpreted as a part of spiritual enlightenment in

Eastern meditative culture[220]. Furthermore, yoga training may transiently increase the intraocular pressure and lead to progressive optic neuropathy, particularly in patients with glaucoma[109]. The musculoskeletal complications, including back, shoulder, or neck pain, osteoarthritis, joint injuries and dislocations, fractures, disc herniation, and tendon deformities have been reported as a common adverse effects of yoga practice[221-223]. However, the frequency of severe injuries associated with yoga is low (less than 5%), and both acute and chronic injuries recover fully[224,225]. Moreover, there are several reports of peripheral nerve injuries after a yoga practice, particularly in the elderly subjects who take sedative medications and patients with hypermobility of the connective tissue[104-106].

CONCLUSION

Most scientific publications on yoga deal with the efficacy of said programs to gain an understanding of the subject to counsel patients appropriately. However, the usefulness of meditation specifically for clinicians, as an occupation group that is particularly associated with physical and mental health risks, still needs more accurate evidence. Although most investigations are in favor of the beneficial effects of yoga on neuropsychological disorders, some studies have not found this meditative procedure useful.

Several points in the studies that have shown the beneficial impacts of yoga on neuropsychological disorders have to be taken into consideration. Multiple investigations reporting beneficial effects of yoga on neuropsychological disorders were not precise in design, implementation, and analysis. There was considerable heterogeneity among the description of yoga interventions in different studies. Different yoga types and many disciplines within the practice have been conducted with various duration and frequency of training. Differences in yoga approaches and the use of different outcome measurements may explain why the outcome of yoga interventions often differed in patients with a common pathological circumstance.

Furthermore, many of these studies have several limitations, such as small sample sizes, short-term follow-up, confounding variables, and lack of appropriate controls. Heterogeneity of intervention procedures and poor qualities of the original investigations substantially influence the value of the meta-analyses that evaluated the effects of yoga on various disorders. Several studies evaluated the underlying mechanism of action of yoga on neuropsychological disorders. However, the exact mechanisms remain to be further elucidated.

Although yoga is a complex approach and difficult to standardize, it is crucial to distinctly describe the intervention procedures, both conceptually and operationally, and avoid excessive heterogeneity[226,227] to consider them as an integrative method in treatment plans for neuropsychological disorders[228]. Furthermore, accurate selection of populations and controls is of great importance to evaluate the potential benefit of yoga on patients with neuropsychological diseases.

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World J Psychiatr 2021 October 19; 11(10): 774-790

DOI: 10.5498/wjp.v11.i10.774

ISSN 2220-3206 (online)

REVIEW

'Omics' of suicidal behaviour: A path to personalised psychiatry

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Author contributions: Videtic Paska A and Kouter K organized and planned the manuscript; Kouter K wrote a part of MS regarding use of omics in suicidal behaviour research: Epigenomics, proteomics, and building the bridge between personalised medicine and psychiatry; Videtic Paska A wrote the introduction, use of omics in suicidal behaviour research: Genomics, metabolomics; all authors approved the final version of the manuscript; Kouter K and Videtic Paska A declare equal contribution to this manuscript.

Supported by the Slovenian Research Agency Research Programme, No. P1-0390, No. J3-7132, and No. Z3-2653.

Conflict-of-interest statement: Nothing to declare.

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Abstract

Psychiatric disorders, including suicide, are complex disorders that are affected by many different risk factors. It has been estimated that genetic factors contribute up to 50% to suicide risk. As the candidate gene approach has not identified a gene or set of genes that can be defined as biomarkers for suicidal behaviour, much is expected from cutting edge technological approaches that can interrogate several hundred, or even millions, of biomarkers at a time. These include the '-omic' approaches, such as genomics, transcriptomics, epigenomics, proteomics and metabolomics. Indeed, these have revealed new candidate biomarkers associated with suicidal behaviour. The most interesting of these have been implicated in inflammation and immune responses, which have been revealed through different study approaches, from genome-wide single nucleotide studies and the micro-RNA transcriptome, to the proteome and metabolome. However, the massive amounts of data that are generated by the '-omic' technologies demand the use of powerful computational analysis, and also specifically trained personnel. In this regard, machine learning approaches are beginning to pave the way towards personalized psychiatry.

Key Words: Epigenomics; DNA methylation; Micro-RNA; Genome; Metabolome; Suicide

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Core Tip: Suicide is major public health concern worldwide, and at the same time, it is preventable when timely measures are taken. The biological basis of suicidal behaviour is not a product of a single gene, transcript, protein or metabolite; rather, it is represented by intertwined cellular mechanisms, cell types and tissue changes, and based on numerous molecular pathways. The '-omic' technologies might represent the missing link between the current state of psychiatry and future personalised approaches, through the combination of -omics-derived information and the diagnostic process. However, first we need precise, specific and validated biomarkers.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Slovenia

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 27, 2021
Peer-review started: February 27, 2021
First decision: July 15, 2021
Revised: July 16, 2021
Accepted: August 30, 2021
Article in press: August 30, 2021
Published online: October 19, 2021

P-Reviewer: Lei XH
S-Editor: Fan JR
L-Editor: A
P-Editor: Guo X

Citation: Kouter K, Videtic Paska A. 'Omics' of suicidal behaviour: A path to personalised psychiatry. *World J Psychiatr* 2021; 11(10): 774-790
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/774.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.774

INTRODUCTION

The International Human Genome Sequencing Consortium published the first draft of the human genome in 2001[1,2]. It was completed in 2003, and it provides information on the human genome structure, organization and variation, as well as on the functions of the complete set of human genes. This determination of the 'blueprint' of the human being represented a major breakthrough for biological and medical research, and importantly, it contributed to the development of contemporary technologies for whole-genome studies[3]. Since then, the expectations in the field of molecular genetics of human diseases have been high for the tackling of the basic causes of numerous polygenic and multifactorial diseases. This also applies to psychiatric disorders and suicidal behaviour.

In the era of the continuing evolution of personalised and precision medicine, data on a patient's genetic background represent the foundation for further decisions on their disease diagnosis, treatment and monitoring, and also for disease prevention[4]. A better understanding of the roles of genetic variations in health and disease would benefit greatly in psychiatry, as psychiatric clinical evaluation currently relies on the clinical interview alone.

Suicidal behaviour

Suicidal behaviour is one of the major global public-health concerns, as every year it accounts for more than 800000 deaths worldwide. In other words, suicides account for 50% of all violent deaths in men, and 71% in women[5]. Suicidal behaviour includes suicide attempts and completed suicides, and its ethology is complex. Many different factors contribute and shape suicidal behaviour, ranging from, but not limited to, biological (genetic, epigenetic), psychological (personality traits), clinical (psychiatric disorders), social and environmental factors[6]. The multifactorial nature of suicidal behaviour demands simultaneous inclusion of many different aspects to deepen our understanding of this phenomena.

The first clues for genetic implications in suicidal behaviour were based on family, twin and adoption studies, and the heritability of suicidal behaviour was estimated to be from 38% to 55% of all attempted and completed suicides[7]. A family history of suicidal behaviour has been recognized as biological, and as a psychological risk factor for suicidal behaviour, independent of psychopathology. This has been supported by small studies[8-12] as well as by a large population study[13]. Impulsive-aggressive behaviour is considered as an endophenotype for suicide, and its familial transmission has been associated with elevated suicide risk in families[14,15]. Twin and adoption studies have provided useful contributions for further estimate of the genetic *vs* environmental factors. Monozygotic twins have shown higher suicide risks than dizygotic twins[13,16], while in studies of suicidal behaviour and adoption, the biological parents had similar effects on suicides in their offspring in non-adopted and adopted situations[17,18].

Rise of the -omics

Initially, the search for genetic biomarkers of suicidal behaviour was based on a candidate gene approach, which was mainly oriented towards neurotransmitter systems, with stress on the serotonergic system. The reason for this stemmed from neurobiological studies that determined the potential characteristics of suicidal behaviour on different body fluids (*e.g.*, blood, cerebrospinal fluid) and *post-mortem* brain. These studies investigated the roles of the serotonergic, noradrenergic and dopaminergic neurotransmitter systems in suicide, as well as signal transduction pathways and cellular morphology[19].

The first genetic studies of suicidal behaviour showed that two genes involved in the serotonergic pathway appear to be involved in suicide vulnerability: Those for tryptophan hydroxylase 1 and serotonin transporter[20]. However, none of the many studies on candidate gene approaches that followed have provided an answer for the genetic variations that lead to suicidal behaviour. From studies on psychiatric disorders, it became apparent that as in other complex diseases, the genetic contri-

bution to such disorders is polygenic–it arises through numerous variants from an extensive number of loci, each of which has small effect on the ultimate disease risk [21]. This caused the shift from a hypothesis-driven approach towards the hypothesis-free approach, to search for novel candidate genes and variants.

With the more recent technological advances applied to the human genome across different populations, tenths of millions of genetic variants have been found. It has been shown that typically the human genome differs across 4.1 to 5.0 million sites from the reference human genome. The majority of these differences (99.9%) are single nucleotide polymorphisms (SNPs) and short insertions and deletions[22]. Genome-wide association studies (GWAS) have thus emerged, with the use of microarray approaches that can interrogate hundreds of thousands of SNPs.

As suicidal behaviour is also particularly affected by environmental factors, such as early-life adverse events, studies on the epigenetic background have begun to increase over the last decade. DNA methylation studies are the most numerous, and a substantial part of the 28 million CpG dinucleotide DNA methylation sites are now being interrogated through microarray and sequencing approaches[23].

USE OF -OMICS IN RESEARCH INTO SUICIDAL BEHAVIOUR

Large genetics-based studies of suicidal behaviour currently show great diversity for the phenotypes under study, and as suicidal behaviour varies in terms of the degree of lethality and suicidal intent, it is expected that these variables will have an impact on biomarkers. Therefore, studies on completed suicides, as the most homogenous phenotype, might reduce this variability[24]. However, due to limited access to *post-mortem* samples from suicide victims, these studies are relatively few. Therefore, studies other than gen-'omic' have more frequently focused on different suicidal behaviours, as well as suicidal thoughts and ideation. Frequently, suicidal behaviour is included only as an additional phenotype in what are primarily psychiatric disorder studies, which will sometimes obscure any clear genetic contributions to suicidal behaviour *per se*. Additionally, comparisons of the data obtained are often hindered due to variabilities in study design, which range from large population-based studies, to a two-step training and testing sample design, to small case-control studies of only a handful of patients. Despite this apparent diversity and the frequent lack of power to detect small effect sizes, these studies have still contributed importantly to a better understanding of the molecular-biological mechanisms underlying suicidal behaviour.

Genomics

Only a handful of GWAS have analysed suicide as the primary phenotype[25-29] (Table 1). One of the most unique study designs included more than 4500 DNA samples from consecutive individuals who died by suicide in the state of Utah. These samples were linked to the population database, through which they identified 43 extended families (7–9 generations) with significantly elevated risk for completed suicides. This thus increased the power to identify genomic regions with high-risk variants for suicide, and at the same time reduced the shared environment effects. Out of 207 target genes identified for suicide, 18 were implicated in inflammation and immune functions, which supported previous studies on associations between inflammation and the aetiology of suicide[25,30]. In the second part of this study, they performed follow-up on the identified target regions in an independent population-based analysis, again on completed suicides, and identified four genes: *SP110*, *AGBL2*, *SUCLA2*, and *APH1B*; however, these should be further sequenced to obtain the potential segregating risk variants[25]. A GWAS on a consortium of three different samples did not reveal any SNPs with genome-wide significance ($P < 1.0 \times 10^{-8}$), but still the pathway analysis of the results identified associations with "Cellular Assembly and Organisation", "Nervous System Development and Function", "Cell Death and Survival", "Immunological Disease", "Infectious Disease" and "Inflammatory Response", all of which have been previously shown to be abnormal in suicidal behaviour[26]. In a far smaller study, again, GWAS did not reveal any significant results, but the validation of the GWAS results with a gene expression study identified a cluster of genes involved in neuroimmune function[27].

The most comprehensive study was carried out through a large United Kingdom biobank for a general population cohort that included over 500000 people, and it covered four suicidality phenotypes that were defined as the categories of "thoughts that life was not worth living", "ever contemplated self-harm or suicide", "acts of deliberate self-harm not including attempted suicide", "attempted suicide" and "no

Table 1 Genome-wide association studies and completed suicide

Type of -omic	Tissue	Number of samples	Main results	Ref.
Illumina Infinium PsychArray platform v 1.0 (approximately 555000 markers)	Blood	216 suicide cases from extended families	*SP110* (rs181058279), *AGBL2* (rs76215382), *SUCLA2* (rs121908538), *APH1B* (rs745918508)	Coon *et al* [25], 2020
llumina Omni1-Quad Beadchip (1014770 markers)	Not stated	577 suicide attempters and suicides, 1233 non-attempter psychiatric and healthy controls	SNPs in *STK3*, *ADAMTS14*, *PSME2*, and *TBX20* genes	Galfalvy *et al* [26], 2015
Affimetrix GeneChip Mapping 50K Xba Array (58900 markers)	Brain tissue	68 suicides, 31 non-suicide deaths	58 SNPs in or near 19 known genes	Galfalvy *et al* [27], 2013
Illumina HumanOmniExpress (733202 markers) and HumanOmniExpressExome BeadChips (273000 markers)	Not stated	Approximately 746 suicides and 14049 non-suicide controls	No genome-wide significant SNP; *GTF2IRD1* locus suggested as associated with age at completed suicide	Otsuka *et al* [28], 2019
Affymetrix United Kingdom BiLEVE Axiom (807411 markers) or the Affymetrix United Kingdom Biobank Axiom (825927 markers) arrays	Blood	> 500000 subjects of different suicide phenotypes and non-suicidal controls	Significant loci for suicidality on chromosomes 9 (*ZCCHC7*), 11 (*CNTN5*) and 13 (rs7989250); genetic correlations between suicidality and depression	Strawbridge *et al*[31], 2019
Illumina Infinium PsychArray platform (593260 markers), Illumina HumanOmniExpress (733202 markers) and HumanOmniExpressExome BeadChips (273000 markers)	Blood	3413 suicides, 14810 controls	Two genome-wide significant loci involving six SNPs: rs34399104, rs35518298, rs34053895, rs66828456, rs35502061, and rs35256367. Additional 52 variants (mapping to 22 genes) with nominal significance	Docherty *et al* [29], 2020

suicidality" controls. A "completed suicides" sub-group was also identified based on death certificates. Generally, a polygenic risk score was observed, but the genetic contributions to different suicidality phenotypes implicated distinct genetic contributions to these categories[31].

Another population based study was performed through an extensive DNA bank of suicide deaths that were merged with medical records and sociodemographic data. This was the first study on completed suicide with sufficient power for a GWAS. Two genome-wide significant loci were identified on chromosomes 13 and 15 that were associated with suicide, and the significant heritability based on the SNPs was estimated to be as high as 25%[29], compared to the heritability of a previous population-based study on suicidality, of 7.6%[31]. The only GWAS on an East Asian population for suicide showed the SNP-based heritability to be 35% to 48%, which again confirmed the polygenic nature of the suicide risk[28].

Several other GWAS have been carried out on other suicidal behaviour phenotypes, rather than completed suicide, and they have most often been studied in association with psychiatric disorders. However, due to the variability of the study designs and the lack of in-depth annotation of the significant variations determined with more comprehensive gene function descriptions, any integration of the results is still missing[32].

Epigenomics

Epigenetics is a rapidly developing field that connects environmental and genetic factors. The term epigenetic regulation broadly covers DNA methylation, histone posttranslational modifications, and regulation by non-coding RNAs[33]. As there is some discussion as to whether non-coding RNAs are truly an epigenetic modification (they show regulation at a post-transcriptional gene expression level), they will be further discussed in the scope of transcriptomics.

DNA methylation is by far the most extensively studied epigenetic modification of suicidal behaviour using candidate gene and -omics approaches. An overview of epigenomic studies that have focused on DNA methylation and suicidal behaviour is given in Table 2. There are multiple approaches to analyse DNA methylation on a genome-wide scale, including whole genome bisulphite sequencing and microarray and antibody-based approaches; these can again make it hard to directly compare studies[34]. The results defined a complex picture of the association of DNA methylation and suicidal behaviour, which included the involvement of differences in cognitive functions[35], cell cycle and cell-cell signalling[36,37], regulation of gene transcription and expression[38], glutamate signalling[39], cell structural integrity and nervous system regulation[40], and neurodevelopment and polyamine metabolism [41].

Table 2 Overview of epigenomic studies that have examined suicidal behaviour

Type of -omic	Tissue	Number of samples	Main results	Ref.
Agilent 400K promoter tiling microarrays	Dentate gyrus	46 suicide completers and 16 comparison subjects	Significantly differential methylation of 366 promoters in suicide victims (273 hypermethylated and 93 hypomethylated)	Labonté *et al* [35], 2013
Illumina Infinium Human Methylation 27 BeadChip	Orbitoprefrontal cortex	25 depressed suicide cases and 28 non-psychiatric sudden death controls	Significantly increased DNA methylation in suicide victims	Haghighi *et al* [36], 2014
Illumina Human Methylation 450 BeadChip	Prefrontal cortex	23 suicide and 35 non-suicide	Significant altered methylation at four CpGs (*ATP8A1*, *SKA2*, *LOC153328* and *KCNAB2* in suicide victims	Guintivano *et al* [37], 2014
Illumina Human Methylation 450 BeadChip	Prefrontal cortex	Six suicide, six non-suicide	Significantly decreased level of methylation in suicide victims	Schneider *et al* [38], 2015
Illumina 450 K Infinium microarray	Prefrontal cortex	22 suicide completers and 28 control subjects	Significantly differential methylation of 454 CpGs in suicide completers	Kozlenkov *et al* [47], 2017
Methylation binding domain-2 (MBD2) sequencing	Prefrontal cortex	22 suicide cases and 17 controls	Significantly decreased methylation in suicide victims, with 115 differentially methylated regions	Nagy *et al*[39], 2015
Reduced-representation bisulphite sequencing	Prefrontal cortex and hippocampus	Nine suicide victims and nine controls	Significantly decreased methylation of 63 and 2406 CpGs and increased methylation of 43 and 328 CpGs in prefrontal cortex and hippocampus, respectively	Kouter *et al*[40], 2019
Illumina Infinium Human Methylation 450K BeadChip	Prefrontal cortex	21 suicides and six non-suicides	Significant correlation of 22 CpGs with gene expression in suicide victims	Cabrera-Mendoza *et al* [41], 2020

Finally here, few studies on epigenetic regulation have so far been carried out that have investigated histones and their posttranslational modification. Most of these have focused on targeting selected genes (*e.g.*, H3K27me3 and TrkB[42]; H3K27me3/H3K4-me3 and polyamine system genes[43,44], H3K9me3 and astrocyte connectivity[45]), with limited success. Misztak *et al*[46] (2020) reported a significant increase in H3K27me2 and decrease in H3K9/14ac in the hippocampus and frontal cortex of suicide victims, which might result in lowered brain-derived neurotrophic factor (BDNF) protein levels[46].

Transcriptomics

Gene transcription can be affected by various biological responses that have tight temporal regulation, which can range from very short (milliseconds) to long-lasting (days) effects[47,48]. Initially, studies used microarray-based approaches to study transcriptomics. As hybridisation-based microarrays have some limitations (*e.g.*, they only allow detection of transcripts complimentary to oligonucleotides bound to the array, and they can cause cross-hybridisation), focus has shifted to sequencing-based methods[49]. Additional advantages of sequencing are the possibility to detect alternative splicing, which is especially common in the brain, and the possibility for qualitative analysis[50].

An overview of transcriptomic studies that have examined suicidal behaviour is given in Table 3. The term transcriptomics refers to the study of all of the coding (*i.e.*, producing a code for a protein output) and non-coding (*i.e.*, providing additional regulatory mechanisms) RNA. As the field of non-coding RNAs is particularly diverse, we will focus on micro-RNAs (miRNA) only. The transcriptome of a given cell often exhibits high tissue specificity, which might be why studies have generally focused on transcriptome analysis of the brain. For suicide victims, changes in mRNA expression have been observed for many processes and pathways, which have included cell–cell communication, signal transduction, cell proliferation, development of the central nervous system[51,52], myelination[53] and microglial functions[54]. Changes have also often been observed for neurotransmission [*e.g.*, glutamatergic and gamma-aminobutyric acid (GABA)ergic signalling[53,55]] and for immune system responses and inflammation[52,54,56].

The search for miRNAs that might be used as biomarkers has not been successful yet, although various miRNAs have been identified as differentially expressed in suicide victims. However, such indications have often not been reproduced in other studies. For example, two studies identified miR-330-3p as differently expressed in suicide victims, with one reporting down-regulation in the prefrontal cortex[57], and

Table 3 Overview of transcriptomic studies that have examined suicidal behaviour

Type of -omic	Tissue	Number of samples	Main results	Ref.
U133A Oligonucleotide DNA Microarrays	Prefrontal cortex	19 depressed–suicide victims and 19 controls	No significant results	Sibille *et al* [105], 2004
Illumina Sentrix HumanRef-8 Expression BeadChips	Orbitofrontal cortex	11 suicide victims and ten controls	Significant downregulation of 59 genes and upregulation of 65 genes in suicide victims	Thalmeier *et al*[51], 2008
Human Genome U133 Set (HG-U133 A and B) microarray	Prefrontal cortex	16 depressed suicides, eight non suicides and 13 controls	Significantly altered expression of 267 genes, associated with cell cycle control and cell division, myelination, ATP biosynthesis and GABAergic neurotransmission in suicide victims	Klempan *et al*[53], 2009
HG-U133AB chipset	17 brain areas (amygdala, hippocampus, nucleus accumbens and 14 Brodmann areas)	26 suicide cases and 13 controls	Altogether over 4000 differentially expressed genes, association with cell communication and synaptic transmission in suicide victims	Sequeira *et al*[55], 2009
RNA-seq	Prefrontal cortex	21 major depressive disorder suicides, 9 MDD non-suicides and 29 controls	Significantly altered expression of 35 genes in suicide victims, association with microglial and immune system functions, and angiogenesis	Pantazatos *et al*[54], 2017
RNA-seq	Hippocampus	17 MDD suicide victims and 23 control subjects	Significant change in expression of 26 genes in depressed suicide victims, association with inflammation and chromatin regulation	Mahajan *et al*[56], 2018
RNA-seqc	Insula	52 mood disorder suicide victims and 45 non-mood disorder controls	Significant downregulation of 20 genes associated with inflammation response, protein- protein interaction, neurodegeneration, neurodevelopmental and upregulation of 5 genes, associated with intracellular protein transport, inflammation, apoptosis regulation and embryonic development in mood disorder suicide victims	Jabbi *et al* [52], 2020
RNA-seq	Prefrontal cortex	17 depressed suicide victims and 17 controls	Significant change in cell-type specific expression in depressed suicide victims	Nagy *et al* [60], 2020
TLDA based miRNA profiler	Prefrontal cortex	18 antidepressant-free MDD suicide victims and 17 controls	Significant downregulation of 21 miRNAs in suicide victims, miRNAs associated with nuclear proteins, transmembrane and signalling proteins	Smalheiser *et al*[106], 2012
LNA-based miRNA profiler	Prefrontal cortex	Four suicide victims and 4 controls	Significant upregulation of a single miRNA, targeting TrkB-T1, observed in low TrkB-T1 expression suicide victims	Maussion *et al*[107], 2012
TLDA-based miRNA profiler	Prefrontal cortex	18 suicide victims and 40 control subjects (all mood disorder)	Significant downregulation of 6 miRNAs and upregulation of 2 miRNAs in suicide victims	Smalheiser *et al*[57], 2014
Small RNA-seq	Prefrontal cortex	Nine suicide victims with depression, nine suicide victims and nine controls	No significant results	Pantazatos *et al*[54], 2017
TLDA-based miRNA profiler	*Locus coeruleus*	Nine suicide victims with depression and 11 controls	Significant upregulation of 10 miRNAs and downregulation of 3 miRNAs in suicide victims. Identified miRNAs are targeting multiple genes that were previously associated with psychiatric disorders	Roy *et al* [58], 2017

the other reporting up-regulation in the *locus coeruleus*[58]; this again indicates the potential importance of tissue specificity.

Recently, focus has been shifting from whole tissue homogenates towards single-cell transcriptome analysis, to better define the complexity of the brain structure and its cellular composition. In doing so, large differences have been seen between subtypes of brain cell populations[59]. Nagy *et al*[60] (2020) analysed the nuclei of the prefrontal cortex in depressed suicide victims, and they identified 26 distinct cell types. The most notable changes were in the deep layer of excitatory neurons and immature oligodendrocyte precursor cells. More specifically, there was association with fibroblast growth factor signalling, steroid hormone receptor cycling, immune function, and cytoskeletal regulation[60].

Proteomics

The proteome is defined as the complete set of proteins that are expressed by a cell or tissue type, or an organism, under specific conditions, which includes proteins that

result from alternative gene splicing, and posttranslational modifications of proteins [61]. The proteome can thus provide us with a snapshot view of the key players in many cellular processes. Compared to transcriptomics, proteomics has the advantage of providing additional information on RNA–protein translation, protein localisation, protein posttranslational modification, protein localisation, speed of protein production and degradation, and interactions with other proteins[62].

Compared to previously described -omics studies, large-scale studies of proteins are not as common when it comes to suicidal behaviour. An overview of proteomic studies that have examined suicidal behaviour is given in Table 4. Usually, protein samples are first separated (*e.g.*, two-dimensional gel electrophoresis to separate proteins based on molecular weight and isoelectric point), with mass spectrometry used to identify a protein of interest[63].

Various tissue samples have been used to date to study the proteomics of suicidal behaviour, including the prefrontal cortex[64-66], amygdala[65] and cerebellum[67]. Studies have also examined cerebrospinal fluid[68,69] and plasma[70,71], as although these are still invasive, they represent more easily accessible sources of tissue.

A reoccurring pattern can be observed, that is similar to the other -omics studies described above. Here, too, there are connections with many of the previously mentioned cell functions and pathways, with indications of association with glial function, neurodegeneration, oxidative stress, neuronal injury[64], the cytoskeleton, synaptic functions[65], coagulation and inflammation[70], decreased glucose utilisation[69], altered cholesterol metabolism in deliberate self-harm[71], transport functions and cell communication in schizophrenia suicide victims[67], the GABA receptor signalling pathway, and pathways related to other neurotransmitters in mood disorder suicide victims (*e.g.*, serotonin receptor signalling, melatonin signalling, CREB signalling in neurons, dopamine receptor signalling)[66].

Additionally, Cabello-Arreola *et al*[66] (2020) reported a reduction in the protein coded by *KCNQ3* (potassium voltage-gated channel subfamily Q member 3) in suicide victims. This protein serves as a building block for the M-channel, a slow working potassium channel that is involved in the regulation of neuron excitability, which has previously been associated with epilepsy, attention deficit hyperactivity disorder, and psychiatric disorders[72].

Suicidal behaviour is often presented as a comorbidity that is accompanied by other psychiatric disorders that have their own specific aetiologies. A study by Vidal-Domènech *et al*[67] (2020) demonstrated this problem. After comparison of cerebellum protein expression of suicide victims with schizophrenia and healthy controls, 99 proteins were identified as significantly altered. During the further validation of three proteins in a larger group of people, including non-schizophrenia suicide victims, only one of these remained associated with suicidal behaviour. This opens the question of whether the 99 proteins identified indicated associations with schizophrenia, suicidal behaviour, or both[67]. Similar considerations should be taken when interpreting other studies, including with patients with identified psychiatric or other disorders.

Metabolomics

Although the most pronounced changes in suicidal behaviour take place in the brain, the access to the brain itself is generally only through *post-mortem* studies. Finding biomarkers for suicidal behaviour that can be repeatedly and easily monitored in real time is therefore aimed at peripheral tissues, like cerebrospinal fluid, platelets, serum and urine, among others, where the intermediate or end products of metabolism can be measured. Among the first clues for metabolites as potential biomarkers for suicidal behaviour was the finding of Asberg *et al*[73] (1976). In the cerebrospinal fluid of depressed suicide attempters they reported that low levels of 5-hydroxyindoalacetic acid (a metabolite of serotonin degradation) were associated with more attempted suicides and with more violent means, compared to patients with high levels of 5-hydroxyindoalacetic acid[73].

An advanced study of metabolites in large numbers is defined as metabolomics. The patterns of metabolic intermediates can be used to determine dysfunctionalities in metabolic pathways, which can be linked to symptomatic presentation[74]. Studies of metabolomics and suicidal behaviour alone have not been performed yet, and have instead been incorporated into studies of psychiatric disorders, and most commonly, depression.

In a multicentre study on the severity of depression and suicidal ideation, plasma metabolites and a machine learning approach were used to build a model to discriminate between depressive patients without and with suicidal ideation. In this study, positive correlation between citrate and suicidal ideation was seen, while negative correlation was seen for kynurenine pathway metabolites (especially

Table 4 Overview of proteomic studies examining suicidal behaviour

Type of -omic	Tissue	Number of samples	Main results	Ref.
2D gel electrophoresis	Cerebrospinal fluid	Seven suicide attempter and seven non-attempters	Significantly altered level of a single protein in suicide attempters. Due to limited amount of material the protein could not be identified	Brunner *et al* [68], 2005
2D gel electrophoresis and MALDI TOF MS	Prefrontal cortex	17 suicide victims and 9 controls	Significantly altered levels of three protein: An isoform of the common astroglia marker glial fibrillary acidic protein (GFAP), manganese superoxide dismutase (SOD2) and α crystallin chain B (CRYAB)	Schlicht *et al* [64], 2007
DIGE qTOF tandem MS	Prefrontal cortex and amygdala	Six suicide victims and six controls	59 significantly altered protein levels in the cortex and 11 significantly altered proteins in the amygdala. Level of nine proteins were significantly altered in both brain regions, but with varying direction of change (either increased or decreased in suicide victims), suggesting the global change in the brain, yet highlighting the importance of tissue specificity	Kékesi *et al*[65], 2012
2D gel electrophoresis and-MALDI-TOF MS	Plasma	12 suicide attempters, 12 MDD patients and 12 controls	Significant change in 45 protein, enabling the differentiation between MDD patients exhibiting suicidal behaviour and non-suicidal MDD patients	Yang *et al*[70], 2016
HPLC and Ion Trap MS	Cerebrospinal fluid	Two suicide victims and two controls	69 proteins with significant change in suicide victims, association with dysregulation of glucose metabolism and oxidative stress response.	Semancikova *et al*[69], 2018
2D-gel electrophoresis and MALDI MS	Plasma	10 self-harm subjects and 18 controls	Downregulation of apolipoprotein A-IV (Apo A-IV) in deliberate self-harm subjects.	Mathew *et al* [71], 2019
Liquid chromatography and tandem MS	Cerebellum	Four suicide victims and four controls	99 significantly altered proteins in schizophrenia suicide victims, association with transport function and cell communication. Vacuolar-type proton pump ATPase (VPP1) further validated and associated with suicidal behaviour.	Vidal-Domènech *et al*[67], 2020
ESI-MS/MS	Dorsolateral prefrontal cortex	Five suicide victims and five controls	33 proteins with significant change in expression (24 decreased and nine increased in the suicide group). Biggest change observed in reduction in protein coded by *KCNQ3* (potassium voltage-gated channel subfamily Q member 3) in mood disorder suicide victims.	Cabello-Arreola *et al*[66], 2020

kynurenine and 3-hydroxykynurenine). Using only citrate and kynurenine, an algorithm for suicidal ideation grade was built[75]. This is of particular interest, as previous studies have associated the tryptophan-kynurenine pathway with brain inflammation and microglial activation, and more recently with suicide[76,77]. In another study of suicidal ideation that was performed on depressed antepartum women, significant inverse associations with suicidal ideation were shown for the neurotransmitter precursors for serotonin and dopamine: 5-hydroxytryptophan and phenylalanine, respectively[78]. Here, again the microglia activation hypothesis might serve as an explanatory mechanism, as it has been linked to alterations in tryptophan signalling and suicidal ideation[77,78]. Of interest, among the metabolomic studies there was also one on cerebrospinal fluid and the serum metabolome. This included treatment-refractory depressed patients, for whom cerebral folate deficiency was shown, although their serum folate levels were normal. In these cases, the metabolomic analysis revealed this reason for the lack of treatment response, which would not have been identified through any other conventional clinical, diagnostic or therapeutic approaches. Administration of folic acid reduced the symptoms of depression, and also the suicidal ideation[74].

Although studies of the metabolome and mental disorders are still in their infancy, these results show great potential for their use, particularly when common treatment approaches do not achieve satisfactory effects.

BUILDING THE BRIDGE BETWEEN PERSONALISED MEDICINE AND PSYCHIATRY

Throughout this review, we have presented the large body of work that has investigated suicidal behaviour, which has ranged from the genome all the way to the metabolome, thus demonstrating further the complexity of suicidal behaviour. A

biological basis of suicidal behaviour can therefore not be determined by any single gene, transcript, protein or metabolite, as it is the final sum of intertwined cellular mechanisms, cell types and tissue changes.

In these current times of the coronavirus disease 2019 (COVID-19) pandemic, the importance of novel approaches to diagnosis and treatment of people with psychiatric disorders is probably greater than ever. An important advance has been the increased use of telepsychiatry, which uses audiovideo technology to enable live interactions, which can be combined with previously prepared materials to provide the needed counselling, monitoring and therapy[79]. However, when it comes to tailoring the approach to the individual and the use of biological markers to diagnose or monitor treatments, great challenges still remain[80]. Psychiatry remains a field of medicine that is heavily dependent on arbitrary determined thresholds of standards, manuals and questionnaires to diagnose and monitor a patient. Not knowing the definitive cause of complex disorders prevents healthcare personnel from treating each patient in terms of his or her full needs. By personalising the care of people with suicidal behaviour and other psychiatric disorders, psychotherapy and drug treatments will improve from the current estimate of 50% success[81,82].

Personalised psychotherapy and pharmacogenomics

Suicidal behaviour and psychiatric disorders are often associated, but they are not exclusively bound together. While some studies have shown that the majority of suicide victims are, or could be, diagnosed with additional psychiatric disorders, it is estimated that only around 5% to 8% of people with psychiatric disorders will exhibit suicidal behaviour[83]. Thus, more suitable drugs and prescriptions would help a large segment of people with suicidal behaviour (as well as the non-suicidal patients).

Pharmacogenomics is a novel field that is studying the genetic basis of drug metabolism and response. The way we metabolise a drug can be greatly influenced by genetic variations, in terms of genes that code for enzymes, drug transporters and other proteins involved in drug metabolism[84]. The most commonly used phenotype classification system divides patients into subgroups of ultrarapid metabolisers, rapid metabolisers, normal metabolisers, intermediate metabolisers, and poor metabolisers [85].

The suitable choice of psychopharmaceuticals and their dosing is often a long process, with patients reporting side effects before the correct doses and drug combinations can be achieved[86]. Multiple enzymes are associated with differences in drug metabolism, with CYP2D6 and CYP2C19 being the most promising in the field of psychiatry. These both belong to the cytochrome P450 superfamily of enzymes that are responsible for drug metabolism. Based on the Pharmacogenomics Knowledgebase (PharmGKB) database, there are currently 17 antidepressants and 10 antipsychotics on the market. These have medical agency approved guidelines and the labels recommend genetic testing for CYP2D6 and CYP2C19. They then offer either selection or dosage recommendations based on the individual metabolic status[86].

While some studies have shown the association of other genetic variants with pharmacodynamics [*e.g.*, *SLC6A4, COMT, BDNF*; as detailed in a review by Lett *et al* [87] (2016)], recent guidelines from the International Society of Psychiatric Genetics do not support their use for prescribing psychiatric medications[86].

Despite its limitations (*i.e.*, test result interpretation, cost, high turnaround time, bias through focusing on European ancestry, population allele frequencies) pharmacogenomics has shown great potential, and might therefore be effective and safer for drug prescribing, such that they can be tailored to the personal genetic makeup of the patient[86,88].

Use of artificial intelligence

These -omic-based studies can provide us with large amounts of data. Artificial intelligence is an approach that is beginning to be increasingly used in various fields of medicine, including psychiatry[89]. Through the use of artificial intelligence, computer models can more easily analyse these large datasets, and more importantly, artificial intelligence can lead to predictions of the risk of an event or disease, based on previously analysed data. To date, artificial intelligence has been used in research into suicidal behaviour that has ranged from analysis of social media texts[90] and health records[91], to analysis of the previously described -omics approaches.

Machine learning algorithms have been successfully used to determine whether a person belongs in the group of suicide attempters or non-attempters with 67% accuracy; this was based on only three SNPs: In *HTR1E* (5-hydroxytryptamine receptor 1E); *GABRP* (g-aminobutyric acid type A receptor subunit Pi); and *ACTN2* (actinin α2) [92]. Based on gene expression and DNA methylation, Bhak *et al*[93] (2019)

successfully differentiated between suicide attempters and patients with major depressive disorder with 92.6% accuracy, and between suicide attempters and control subject with 86.7% accuracy[93]. Similarly, metabolic profiles can be used to try and differentiate between people. A study by Setoyama *et al*[75] (2016) associated the kynurenine pathway metabolites and citrate with suicidal ideation, which allowed determination of the patients without and with suicidal ideation[75].

An interesting study was reported by Just *et al*[94] (2017), where they used functional magnetic resonance imaging to provide an insightful view of the differences of concept understanding. By measuring the changes in brain activity when presented with words or concepts, the locations and intensity of the responses differed between people with suicidal ideation and the control group; this model differentiated between these two groups with 91% accuracy[94].

Although artificial intelligence comes with several limitations, such as the need for large amounts of unbiased data, precise model development, and technical abilities, it appears to hold promise of better treatment possibilities of individuals. Artificial intelligence should provide better understanding and detection of suicidal behaviour and suicidal ideation, aid in therapy progression and treatment planning, and help with patient monitoring and stratification[95].

Challenges of personalised medicine

Psychiatric disorders are highly heterogeneous, with complex biological underpinning, paired with additional cultural, social and environmental factors[96]. Bragazzi[96] (2013) proposed the use of "psychiatome" to combine the interactions of all of the -omics involved in the development of the psychiatric state of a person. This covers genes, transcription and protein networks, along with brain anatomy, and should incorporate the concept of '5P' medicine: personalised, participatory, predictive, preventive and psycho-cognitive[96]. These -omics might represent part of the missing link between the current state of psychiatry and future personalised approaches, through the addition of -omics-derived information to the diagnostic process. However, for this we need precise, specific and validated biomarkers, which have not yet been identified. Additional limitations of personalized medicine in psychiatry include the question of stigma (*e.g.*, effects on the general population, patients and public health policy makers), ethical aspects (*e.g.*, conflicts of interest, informed consent of patients, data protection), cost-effectiveness and need for additional skillsets for healthcare providers[97].

By including -omics-based data in the diagnostic process, psychiatric disorders can be viewed as spectrum disorders, instead of the current binary "disease or health" approach that is proposed by psychiatric manuals[98]. Here, the end goal is not to reject the classical definition and the diagnostics and care of psychiatric disorders, but to compliment these with better understanding of each patient group[99].

CONCLUSION

Suicide is devastating, but at the same time it is preventable if timely measures are taken. Therefore, understanding the biological background of suicide is important, to help develop clinically applicable tools for its detection. However, like in many other cases of complex diseases, we are only just beginning to uncover the biological clues for its development.

Candidate gene approaches and GWAS still lack the identification of any common gene or variant. None of the most researched genes in suicidal behaviour, the serotonergic genes, have been replicated in any GWAS on suicidal behaviour[100]. The replication of results is affected by significant sample differences (*e.g.*, demographic characteristics, primary diagnosis, suicidal behaviour/ideation phenotype) and methodological approaches (*e.g.*, candidate genes, GWAS) across studies. Microarrays are being gradually supplemented and replaced with novel sequencing approaches that can produce faster and cheaper information, which will lead to the generation of more medically useful information, like whole exome sequencing. However, in the case of mental health, we are still far away from any molecular-based tool that is useful for clinical prediction. Only single studies on suicide and whole exome sequencing are currently available[101], and although several hundred thousand SNPs and insertions/deletions have been identified, currently these data provide 'only' a resource for further laborious in-depth analysis to find further biologically meaningful information.

In recent years biomarker research has started to uncover the intriguing roles of extracellular vesicles. These small vesicles are excreted by virtually all cells, and they are involved in cellular communication, as they can travel over short or long distances. Their crossing of the blood–brain barrier gives them particular value in research into the central nervous system, as extracellular vesicles are defined by their origin and their cargo (*e.g.*, proteins, DNA, RNA). This opens new potential for peripheral markers for brain disorders[102]. In the field of metal disorders, only a few studies have been performed, while their involvement in research into suicidal behaviour is currently still untouched[103]. Determination of the origin, number and content of extracellular vesicles, can provide an important contribution to our understanding of brain function in a state of severe stress, such as inflammation or an immune response, both already associated with suicidal behaviour. As the current COVID-19 pandemic represents a significantly increased risk of sociological risk factors for suicidal behaviour, the disease itself triggers inflammation and extremely strong immune responses with a cytokine storm, which can promote increased risk of psychiatric disorders, chronic trauma and stress, which in turn will increase suicide and suicidal behaviour[104]. From this point of view, this represents a unique opportunity to perform molecular-genetic studies on suicidal behaviour using cutting-edge technology.

ACKNOWLEDGEMENTS

The authors thank Dr. Christopher Berrie for scientific English editing of the manuscript.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 791-804

DOI: 10.5498/wjp.v11.i10.791

ISSN 2220-3206 (online)

MINIREVIEWS

Environmental pollution with psychiatric drugs

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Author contributions: All authors participated in the work to take public responsibility for its content, provided substantial contributions to conception and design of the manuscript, contributed to drafting the article and revising it critically for important intellectual content and provided final approval of the version that was submitted.Both Julene-Argaluza and Saioa Domingo-Echaburu contributed equally to the work.

Conflict-of-interest statement: The authors declare no conflicts of interest.

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Abstract

Among all contaminants of emerging interest, drugs are the ones that give rise to the greatest concern. Any of the multiple stages of the drug's life cycle (production, consumption and waste management) is a possible entry point to the different environmental matrices. Psychiatric drugs have received special attention because of two reasons. First, their use is increasing. Second, many of them act on phylogenetically highly conserved neuroendocrine systems, so they have the potential to affect many non-target organisms. Currently, wastewater is considered the most important source of drugs to the environment. Furthermore, the currently available wastewater treatment plants are not specifically prepared to remove drugs, so they reach practically all environmental matrices, even tap

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 23, 2021
Peer-review started: February 23, 2021
First decision: June 18, 2021
Revised: June 18, 2021
Accepted: August 31, 2021
Article in press: August 31, 2021
Published online: October 19, 2021

P-Reviewer: Hosak L, Seeman MV
S-Editor: Wu YXJ
L-Editor: A
P-Editor: Yu HG

water. As drugs are designed to produce pharmacological effects at low concentrations, they are capable of producing ecotoxicological effects on microorganisms, flora and fauna, even on human health. It has also been observed that certain antidepressants and antipsychotics can bioaccumulate along the food chain. Drug pollution is a complicated and diffuse problem characterized by scientific uncertainties, a large number of stakeholders with different values and interests, and enormous complexity. Possible solutions consist on acting at source, using medicines more rationally, eco-prescribing or prescribing greener drugs, designing pharmaceuticals that are more readily biodegraded, educating both health professionals and citizens, and improving coordination and collaboration between environmental and healthcare sciences. Besides, end of pipe measures like improving or developing new purification systems (biological, physical, chemical, combination) that eliminate these residues efficiently and at a sustainable cost should be a priority. Here, we describe and discuss the main aspects of drug pollution, highlighting the specific issues of psychiatric drugs.

Key Words: Antipsychotics; Pharmaceuticals in the environment; Drug pollution; Antidepressants; Wastewater; Ecotoxicity

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Core Tip: Psychiatric drugs have received special attention as contaminants of emerging interest because of two reasons: First, their use is increasing. Second, many act on phylogenetically conserved neuroendocrine systems, potentially affecting many non-target organisms. Drug pollution is a complicated problem involving many stakeholders with different values and interests. Solutions can be applied at source, using medicines more rationally, prescribing greener drugs or designing pharmaceuticals that are more biodegradable. Besides, end of pipe measures, *e.g.*, developing new purification systems will also be crucial. Finally, educating both health professionals and citizens, and collaboration between environmental and healthcare sciences is going to be essential.

Citation: Argaluza J, Domingo-Echaburu S, Orive G, Medrano J, Hernandez R, Lertxundi U. Environmental pollution with psychiatric drugs. *World J Psychiatr* 2021; 11(10): 791-804
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/791.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.791

INTRODUCTION

Toxic problems caused by chemicals, such as aromatic compounds, polychlorinated biphenyls, heavy metals, pesticides, *etc.*, are well known. However, concern regarding the so-called "pollutants of emerging interest" is increasing, with pharmaceuticals causing the greatest concern. Pharmaceutical products have two important characteristics that are driving this preoccupation: Firstly, they produce pharmacological effects at low concentrations, such as those found in the environment. Secondly, they are designed with stability in mind, so they are more likely to reach and interact with their target molecules.

THE PROBLEM OF ENVIRONMENTAL POLLUTION WITH PHARMACEUTICALS

Publications in scientific journals regarding the presence of pharmaceutical products in the environment has grown exponentially since the end of the 1990s, due to improvements in analytical techniques allowing for the detection of lower concentrations of drugs in different matrices[1]. Currently available information regarding the presence of pharmaceuticals in the environment and their consequences is simply

overwhelming.

A recent study estimated that approximately 4000 different pharmacologically active substances are currently being administered globally, including: Prescription drugs for human use, over-the-counter drugs, and veterinary drugs[2]. Global drug use continues to grow, with an estimate of 4.5 trillion doses consumed in 2020[3]. The trend will probably continue for the following reasons[2]: The age and life expectancy of populations has increased; economies are growing, especially emerging economies, so the capacity and expectations to treat aging and chronic diseases increase; intensification of livestock and aquaculture practices to meet demand; the design of new pharmaceutical products; climate change, which will aggravate existing diseases (both communicable and non-communicable).

Psychiatric drugs have received particular attention above other therapeutic classes for two main reasons: Their widespread use and their potential to provoke ecotoxicological damage. Some authors believe the current situation due to the Coronavirus disease 2019 pandemic may lead to an increase use of certain psychiatric drugs, like anxiolytics or antidepressants[4].

Life cycle of drugs

The liberation, absorption, distribution, metabolism, excretion (LADME) scheme showing the curse of drugs in the human organism is still shown in universities across the world. Drugs are first released, then absorbed, distributed, metabolized, and finally excreted outside. But in this anthropocentric scheme, little or no attention is paid to drugs and metabolites once they are excreted outside the organism (Figure 1).

Of course, drugs and their metabolites do not disappear after flushing the toilet, but rather reach the environment in different amounts depending on the proportion metabolized in the body. It has been estimated that the percentage of unchanged drug excreted in feces and urine is between 30% and 90% on average[5].

Any of the multiple stages that make up the life cycle of the drug: production, consumption and waste management; is a possible entry point to the different environmental matrices.

In any case, currently the most important source is considered to be wastewater, which includes wastewater of domestic, hospital, industrial and of agricultural or livestock origin. Pollution due to industrial waste disposal was not considered a major factor until recently. Contemporary research shows, however, that certain production factories can cause environmental pollution at levels well above what was previously thought[6]. For example, very high venlafaxine concentrations were found in a wastewater treatment plant (WWTP) that received the discharge of a large industrial plant near Jerusalem, in Israel[7].

But pharmaceutical products can reach the aquatic environment by other routes, including, for example: aquaculture, runoff water from the agricultural sector, through the removal of sewage sludge (especially when used as fertilizer in agriculture), or leaching to groundwater after rain. Likewise, the presence of pharmaceuticals has to be considered when re-using wastewater in agriculture, a practice that is expected to increase in the near future[8].

The current purification systems: WWTPs

Currently available WWTPs are not specifically designed to remove drugs. Some of them are eliminated, but others remain unchanged and are discharged with the effluents. As an example, a study carried out in the United Kingdom in 2018 estimated that in 13% of the WWTPs available in that country, the effluent contained potentially dangerous concentrations of drugs such as ethynylestradiol, diclofenac, propranolol, macrolide antibiotics and fluoxetine[9]. Sometimes, paradoxically, the drug concentration in the effluent of the WWTP can be even higher than that in the influent. This is due to the microorganisms in charge of the biological (secondary) treatment of wastewater may be in charge of metabolizing the conjugates with glucuronic acid, so that the drug returns to its original form[5]. This is the case with carbamazepine, amitriptyline, lamotrigine, doxepine, citalopram, among many other pharmaceuticals [10]. Besides, a study estimated that up to 70% of all wastewater does not receive treatment before being discharged, so the situation in developing countries is probably even worse[11,12].

Presence of drugs in environmental matrices

Residues of multiple types of drugs (about 700) have been detected in different environmental compartments mainly in wastewater, surface and groundwater, but also in soil, air and biota, even in the tap water that we drink[13]. In the specific case of

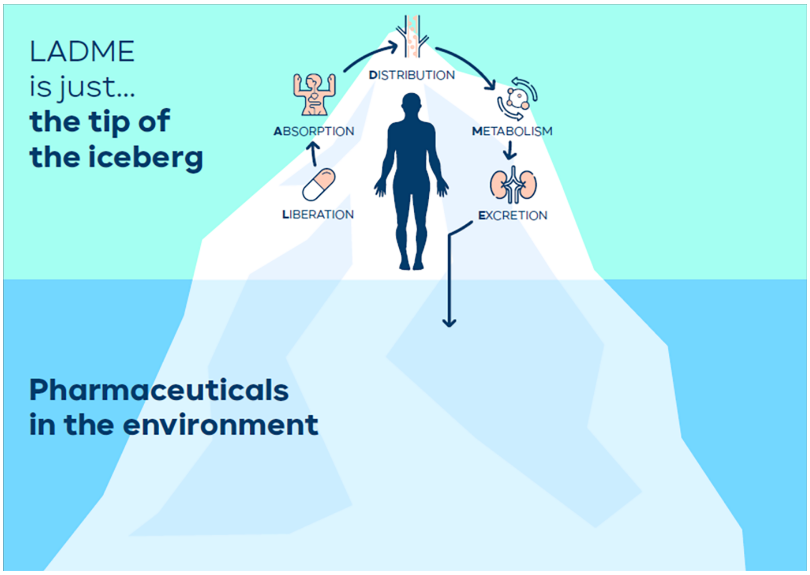


Figure 1 The liberation, absorption, distribution, metabolism, excretion scheme is just the tip of the iceberg. LADME: Liberation, absorption, distribution, metabolism, excretion.

psychiatric drugs, there are complete books reviewing their presence in the environment[14]. Carbamazepine has even been considered as a marker for wastewater influenced water bodies due to its omnipresence[15].

For a greater detail of all the drugs detected in any environmental matrix, the free database of the German Environment Agency can be consulted, which maintains an exhaustive registry of all published studies, available from: https://www.umweltbundesamt.de/dokument/database-pharmaceuticals-in-the-environment-excel.

Furthermore, once they have reached the environment, parent drugs (or metabolites) continue to transform and continue to undergo complex metabolic processes by different organisms as well as by different physicochemical mechanisms (photo-degradation, adsorption to solids, *etc.*), leading to "transformation compounds". For example, Trawiński *et al*[16] reviewed the photodegradation process of psychotropic drugs. Some substances can remain unchanged in the environment for decades, *i.e.*, are very persistent. This is the case of oxazepam, which has remained unchanged at the bottom of Swedish lakes for more than 30 years[17].

Ecotoxicological effects of psychiatric drugs

Toxic effects of drugs in the environment can go far beyond growth, mortality or reproduction. For example, psychoactive drugs can affect organism behaviour and fitness, altering population dynamics[18-21]. The therapeutic targets and the physiological systems in which drugs act are not exclusive to human beings. Many of these structures and signaling pathways are highly conserved phylogenetically, and are present in many living organisms[22]. For example, multiple behavioral tests (such as anxiety, fear and stress) for experimental drugs intended for human use are performed on fish[23]. Fish share many of the neurotransmitter and signaling pathways with us. In fact, biogenic monoamines (serotonin, dopamine, norepinephrine, *etc.*) are found in vertebrates and invertebrates, including amphibians, fish, insects and echinoderms[24,25]. These substances are so ancient from an evolutionary point of view that they are present in organisms outside the animal kingdom. For example, acetylcholine is present in fungi and bacteria[26] and serotonin in plants[27]. Fluoxetine has shown to induce behavioral changes in crickets[28]. Fish also become constipated in the presence of the antipsychotic clozapine[29], plants accumulate benzodiazepines that could act on their GABAergic system[30], or sertraline affects sedimentary nitrification processes by altering the microbial trophic chain[31].

Castillo-Zacarías *et al*[32] have recently reviewed available literature about the presence and effects of antidepressants on the environment. We have also shown that the role of antipsychotic drugs as environmental pollutants has probably been underrated so far[33].

In short, the psychoactive drugs that we use and excrete into the environment can have pharmacological effects in different non-target organisms. However, the extent of exposure and subsequent effects remains unknown for many taxa and ecosystems[34]

(Table 1).

Effects of drug pollution on human health

The effect of drug pollution on human health is still relatively little studied. A WHO report published in 2012 concluded that drug concentrations in tap water should not pose any health problems[35]. These findings were confirmed in a recent study carried out in China[36]. However, the presence of drugs in the environment could be a problem for the most vulnerable groups of patients (*e.g.*, allergic[5]). Although there is no evidence of short-term effects on human health, uncertainties remain, in particular concerning long-term exposure (chronic exposure) to a mixture of pollutants[5]. The possible routes of exposure are, mainly, consumption of drinking water, vegetables and tubers, meat, fish, shellfish and dairy products[5].

Probably the best known example of the deleterious effect of drug pollution on human health is that of the increase in bacteria with resistance to antibiotics, which is currently recognized as the biggest public health problem worldwide. In this sense, we consider that the "One Health" approach or philosophy, which considers that human health is closely interrelated with environmental health, is essential[37]. Nevertheless, we believe that it is necessary to extend this approach to all therapeutic groups including psychiatric drugs, not only antibiotics[38,39].

Some authors have suggested that psychoactive drugs present in the environment may potentially be associated with human neuropsychiatric disorders such as autism, Alzheimer's disease and schizophrenia, since they are able to cross the maternal barriers affecting the development of the embryonic brain[40].

Bioaccumulation

Recent studies suggest that certain drugs bioaccumulate in non-target organisms through the food web, reaching tissue concentrations much higher than those found in the environment. For example, a study carried out in five Australian rivers found that platypuses and brown trouts bioaccumulate 66 of the 80 drugs studied due to their insectivorous diet. First, the larvae of riparian insect's bioaccumulated certain drugs present in surface waters, and subsequently, these drugs can pass to the animals that eat them. Surprisingly, the researchers estimated that, in the case of antidepressants, platypus might be exposed to amounts up to half the daily doses used in humans[41]. (Table 1).

A recent work studied the presence of more than 90 drugs pertaining to 23 different drug classes in blood plasma of wild European fish in three different European countries. For some drugs, measured fish plasma concentrations were above human therapeutic plasma concentrations. Indeed, three of the four drugs that showed a moderate or a high risk of inducing toxic effects on fish were antipsychotics: *i.e.*, risperidone, flupentixol and haloperidol[42].

An excellent review of the bioaccumulation of pharmaceuticals (including psychiatric drugs) in aquatic fish and invertebrates was published by Miller *et al*[43]. Besides, this bioaccumulation process is not exclusively restricted to the aquatic environment. A study carried out in the Doñana National Park, Spain, showed that dung beetles accumulate the antiparasitic ivermectin used in livestock in their tissues. Ivermectin, with recognized insecticidal activity, is toxic to beetles that are in charge of processing manure, in such a way that the properties of the soil are altered[44]. In addition, some studies suggest certain psychiatric drugs like carbamazepine and fluoxetine might bioaccumulate in terrestrial organisms (earthworms) depending on the properties of the soil and the physico-chemical characteristics of the drug[45].

We still understand little about what is happening ... although highly hypothetical, what if insectivorous bats were accumulating drugs in their tissues? What consequences could this have on the appearance of new zoonosis[46]?

Environmental impact risk reports from the European Medicines Agency

Since October 2005, the European Medicines Agency has required the laboratories holding the marketing authorization to assess the environmental impact of medicines [47] (ERA: Environmental risk assessment). Despite this significant progress, this report is not considered during the benefit-risk balance in drug evaluation, even if it shows potential risks for the environment. For example, the ERA of the recently marketed antidepressant vortioxetine[48] recognizes that this drug is "potentially harmful to the environment". Something similar occurs with the antipsychotic asenapine[49], for which the ERA recognizes that it is a potential endocrine disruptor. Despite this, both drugs have been marketed without any restrictions.

Table 1 Examples of the presence of certain psychiatric drugs in the environment and ecotoxicological effects on organisms

Therapeutic class	Drug	Non-target organism	Ecotoxicological effects	Ref.
Antiepileptics	Carbamazepine	Ryegrass (*Lolium perenne*)	Accumulation in plants tissues	Carter *et al*[83], 2014
Antidepressants	Various	Platypus (*Ornithorhynchus anatinus*), Brown Trout (*Salmo trutta*)	Half of human daily dose, insectivorous diet. Effects?	Richmond *et al*[41], 2018
	Sertraline	River sediment microorganisms	Sedimentary nitrification processes by altering the microbial trophic chain	Li *et al*[31], 2020
	Fluoxetine	Cricket (*Gryllus campestris)*	Behaviour disturbance	Abey-Lee *et al*[28], 2018
		Starling (*Sturnus vulgaris*)	Reduced female attractiveness	Whitlock *et al*[84], 2018
Benzodiazepines	Various	Beet (*Beta vulgaris*)	Phitotoxicity	Carter *et al*[30], 2018
	Oxazepam	European perch (*Perca fluviatilis*)	Behaviour and feeding rate disturbance	Brodin *et al*[85], 2013
Antipsychotics	Clozapine	Zebra fish (*Danio rerio*)	Constipation	de Alvarenga *et al* [29], 2017
	Risperidone	Zebra fish (*Danio rerio*)	Alteration of antipredatory behavior, transgenerational effect	Kalichak *et al*[86], 2019
	Various	Chub (*Squalius cephalus*)	Fish plasma concentrations > Human plasma therapeutic concentrations	Cerveny *et al*[42], 2020

At the moment, and contrary to what happens for certain medicinal products for veterinary use, the environmental impact is not taken into account in the benefit/risk balance of the evaluation of medicinal products for human use, which is based solely on criteria of efficacy and safety. We believe that this may change in the future, as we gain knowledge on the environmental risks of medicines[38]. In addition, another aspect to consider is that all drugs marketed before that date (October 30, 2005) are exempt from submitting this environmental impact report in the renewal of their marketing authorization, so the information available about many of the drugs currently used is scarce or non-existent. For some drugs, such as fluoxetine, an ERA is published many decades after its authorization[50]. Another aspect is that current ecotoxicological tests demanded by the EMA do not include behavioral tests. Some authors propose updating the demanded tests in order to incorporate these kind of ecotoxicological tests[21]. Currently, the regulation of ERAs for medicines for human use is under review. It seems that some changes will occur, specifically in terms of bioaccumulation and fundamentally endocrine disruptors[51]. However, the legislation involved in Europe is varied, abundant, complex and not always easy to understand by non-experts in the field[52]. Another important issue is that legislation differs between countries, or is, directly, non-existent[53]. On the other hand, there are veterinary drugs used in pets, for which the environmental impact assessment is not considered in the benefit/risk balance either. There are authors who consider that this should change, taking into account the toxicity of some of the substances used and the increasing number of pets in our environment[54,55].

POSSIBLE SOLUTIONS

The study of the problem of drug pollution is among the priority lines of research of the main organizations dedicated to the protection of public and environmental health, such as the WHO and the European Commission. In this regard, it is worth highlighting the publication of the "Strategic approach of the European Union in the field of pharmaceutical products in the environment" by the European authorities, probably the front-runners in the field[56].

The contamination of the environment with pharmaceutical products is a complicated and diffuse problem that entails scientific uncertainties, a large number of stakeholders with different values and interests, and great complexity. This is probably why the Dutch government has classified it as a "wicked problem" (a

problem that is difficult or impossible to solve given that it presents incomplete, contradictory and changing requirements that are generally difficult to recognize). In their comprehensive strategy to face the problem, they have established that all agents involved in the complex life cycle of the drug should participate in the solution[57].

It is more than likely that in the future, as the detection of drugs and ecotoxicological studies progress, many drugs will end up being a priority in legislative matters, and that maximum concentration of certain drugs in wastewater may be established. We believe that we are on the verge of a revolution in the field of psychopharmacology[38].

At source measures

Before trying to improve the elimination processes of drugs once they reach the WWTP and the environment, it is probably reasonable to act at source. Considering that drugs have offered, and continue to offer, an unquestionable benefit to the health of humanity, great care must be taken not to restrict access to those drugs that are necessary. Here are some ideas that could help improve the problem.

Rational use of the drug, eco-prescription, or "green prescription"

The "Rational use of medicines" is a term coined by WHO experts more than 30 years ago, in 1985[58]. To date, the rational use of medicine has been defined as "patients receive the appropriate medication for their clinical needs, in the doses corresponding to their individual requirements, for an adequate period of time and at the lowest possible cost for them and for the community". This term has served as a conceptual framework of undoubted value to promote actions and strategies that have improved the health of countless patients, avoiding excesses in the use of medications, polypharmacy, *etc.* However, we believe that the term requires an update, so that the "One Health´s philosophy, which tries to achieve optimal health for people, animals and our environment taking into account the existing interrelations, is considered[59]. Currently this philosophy is already applied, but fundamentally to antimicrobials. We believe that broadening the approach is necessary. Reducing the inappropriate consumption of drugs will reduce their entry into ecosystems, improving people's health and that of the environment[60].

Christian Daughton, head of the American Environment Agency, now retired, proposed more than 5 years ago the term "eco-prescription", or "green prescription". Ultimately, it means that the prescriber should consider the characteristics and environmental behavior of drugs when prescribing them[10]. This is definitely going to be challenging. For example, oxazepam (not available in some countries such as Spain, but a common metabolite of numerous benzodiazepines commonly used in our setting), is considered a good choice for the elderly due to its adequate pharmacokinetic profile, since it is not eliminated by oxidative metabolism and is excreted unchanged in urine. However, it is a known to cause of potential toxic effects in fish, and can accumulate for decades without biodegrading. From an environmental point of view, substances that are metabolized to inactive metabolites prior to elimination may be preferable[10]. We believe that incorporating environmental criteria in the use of medicines is essential, and it may become a true revolution in pharmacotherapeutics [38].

Another interesting classification of drugs is the one proposed by the Swedish Environmental Research Institute. It is one of the few available classifications of drugs according to their environmental characteristics. It is an initiative of the Stockholm City Council, driven by the pharmaceutical industry. Each drug receives three scores, each of which can take a value from 0 to 3: one on its persistence in the environment (P); another on bioaccumulation (B) and another on toxicity (T). The overall score is the sum of the points obtained for each item[61].

Prescribers may incorporate this information when using drugs in individual patients. The "Wise List" (*Kloka Listan)*, is so far, the only multifaceted approach incorporating environmental aspects to recommend drugs in ambulatory care[62]. The chain approach of the Dutch Government also incorporates a "psychotropic task force" in order to reduce psychotropics in water[57]. We believe further research is urgently needed in this crucial area.

The design of more biodegradable and sustainable drug: "Green design"

An attractive idea for the future is to design greener and more biodegradable drugs; i: e: "benign by design" concept[63]. Although there are already some examples of the development of more "environmentally friendly" drugs, such as glufosfamide[64] and green drug delivery systems[65], no psychoactive drugs has been designed to be more biodegradable.

Furthermore, a holistic approach should be considered when evaluating the environmental impact of medicines, and other constituent parts of medicines ought to be taken into account apart from active pharmaceutical ingredients. We believe there is room for improvement in this specific area. For example, inhaled loxapine, a recently marketed antipsychotic for the treatment of agitation, requires a lithium battery for each dose administered. Another example would be Abilify Mycite®, in which an electronic circuit is excreted with each capsule administered[38].

Education

Until now, healthcare professionals who are in charge of prescribing, administering and dispensing drugs have paid little attention to the problem of drug contamination, which has been preferentially addressed by biologists, chemists and other professional profiles such as environmentalists. We firmly believe that this concern cannot be ignored anymore in the schools of Medicine, Pharmacy and Nursing[66]. Recent studies carried out in China have shown that awareness of the problem in both pharmacists[67] and prescribers[72] has a wide room for improvement. As proposed in the European Commission strategy[56], we believe that general education for both health professionals and citizens is a key element in the fight against drug pollution.

Improved waste management, responsible consumption

The incorrect management of pharmaceutical waste is one of the routes of entry of medicines into the environment. Studies indicate that up approximately 33% of patients do not use all the medicines dispensed, which generates a waste of health resources and possible environmental contamination[2]. The generalization of the adoption of refund schemes such as SIGRE, implemented in Spain, will be another key element. This is especially important in countries where waste management is not working well and where inappropriate drug disposal can be expected, such as regions form the Middle East, Asian and African countries[69]. Optimizing package sizes and extending drug expiration dates where possible will allow drugs that are still safe to use from being unnecessarily discarded. The idea of reusing drugs has also been proposed. In this regard, a survey conducted in the United Kingdom found that more than half of those surveyed would welcome the reuse of medicines in the future[70]. Although it is not legally accepted in many countries, it could help reduce the amount of unused medicine accumulation, a fact that can lead to overuse or incorrect use of medicines or also to incorrect disposal. However, obviously, considering security issues is mandatory if such policies are going to be implemented.

From a regulatory perspective, the European Parliament suggests that "eco-labeling" of pharmaceutical products with a high risk for the environment should be explored (Figure 2), as is already done with other products in the market[71].

Legislation

As knowledge about the environmental impact of pharmaceuticals keeps mounting up, ERAs need to update accordingly to improve our capability of correctly assessing the risk posed. It is interesting to highlight that last year, venlafaxine and desvenlafaxine were considered as suitable for inclusion in the next "Watch List" (WL): under the European Union Water Framework Directive[72]. These antidepressants are the first psychoactive drugs ever to be included in such a list[73].

End of pipe measures

Apart from implementing at source measures, it is essential to address the problem of waste already generated. Taking into account the growing consumption of drugs at a global level, the research and development of new purification systems (biological, physico-chemical) that eliminate these residues efficiently and at a sustainable cost should be a priority.

Improvement of WWTPs

The design of purification systems requires prior knowledge of the physical-chemical characteristics of the effluent wastewater and of the concentration of the main eliminated drugs, especially those that represent a greater risk for the environment.

For example, in order to optimize costs, various authors propose eliminating drugs at the hospital wastewater effluent instead of treating the total amount of water reaching WWTPs, since hospitals are the main consumers of certain types of pharmaceuticals (some cytostatics, broad-spectrum antibiotics, iodine contrasts). There are already interesting initiatives such as the one implemented at the Herlev Hospital in Copenhagen, Denmark, where improved treatment of hospital wastewater is



Figure 2 Will we see drugs with eco-label?

performed on-site to effectively remove all drugs before they reach the municipal WWTP[74].

Anther strategy is that carried out by Switzerland, a country in which all treatment plants from a certain size are going to be improved (through tertiary treatment with ozone and activated carbon) to effectively eliminate drugs and other emerging contaminants, at an approximate cost of 1 billion euros[75]. However, this strategy is probably not sustainable or applicable to most countries. On the other hand, ozonation can oxidize drugs producing new transformation products with poor known ecotoxicological effects[76].

New methods that improve the performance of WWTPs in the elimination of drugs continue to be studied and sought. A curious method is the use of xylophagous fungi (*white rot fungi*) of which the species most used to date is *Trametes versicolor*. These fungi, in charge of degrading soil organic matter in nature, possess enzymes, called "laccases" with the capacity to oxidize a wide spectrum of organic substances, including drugs[77].

Eco-pharmacovigilance, environmental pharmacovigilance

In the 1960s, the use of thalidomide was used for the treatment of nausea and vomiting in pregnant women. Later, the drug proved to be teratogenic, producing thousands of newborns malformations. This disaster gave rise to the modern pharmacovigilance systems currently in place. Since the ecological disaster produced by diclofenac in the Indian subcontinent, various authors have asked to create a new discipline, *i.e.*, "Eco-pharmacovigilance" or "environmental pharmacovigilance"[78]. This discipline will dedicate to "monitor" the environmental impact of drugs[79]. Will be ever witness a market withdrawal of an antidepressant or an antipsychotic, or any other drug, because of environmental factors in the future? May be.

Phytoremediation

From the point of view of environmental drug contamination, the accumulation of drugs by plants can be harmful (in the case of agriculture) or beneficial, if done on purpose. Phytoremediation is a technology that uses plants and the associated microorganisms of the rhizosphere (zone of interaction between plant roots and soil microorganisms) to eliminate, transform or contain toxic chemicals located in soils, sediments, groundwater and surface waters, among others. Different species of plants have been used for the treatment or removal of a variety of pollutants such as oil, chlorinated solvents, pesticides, metals, radionuclides, explosives and pharmaceuticals [80]. The design of constructed wetlands, a technique than can be employed for the removal of pharmaceuticals from wastewater, has received particular attention[81]. It is interesting to verify that the detoxification mechanisms used by plants, are sometimes surprisingly similar to those of mammals, as in the case of glutathione conjugation of paracetamol in the *Brassica juncea* plant[82].

CONCLUSION

So far, the problem of drug pollution has been largely ignored by healthcare professionals and academics. However, if the problem is to be dealt with effectively, an interdisciplinary approach will be necessary, allowing integration of the knowledge of the different agents involved[38].

In conclusion, drug pollution with psychiatric drugs is a problem of emerging concern. This complex problem involves many stakeholders with different values and interests. Solutions can be implemented at source, before drugs reach the environment: using medicines more rationally, prescribing greener drugs, or designing pharmaceuticals that are more easily biodegradable. Besides, end of pipe measures, such as the development of new, sustainable purification systems will also be crucial. Finally, educating both health professionals and citizens, and collaboration between environmental and healthcare sciences is going to be essential.

ACKNOWLEDGEMENTS

The authors would like to thank A .Vitoria-Gasteiz and F.Vital for their support.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 805-820

DOI: 10.5498/wjp.v11.i10.805

ISSN 2220-3206 (online)

MINIREVIEWS

Connecting brain and body: Transdiagnostic relevance of connective tissue variants to neuropsychiatric symptom expression

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Author contributions: Sharp HEC, Critchley HD and Eccles JA equally shaped the ideas and structure of this review; Sharp HEC searched the relevant literature and took the lead in writing the manuscript; Sharp HEC, Critchley HD and Eccles JA provided full input to and critical feedback of the final manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

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Abstract

The mind is embodied; thoughts and feelings interact with states of physiological arousal and physical integrity of the body. In this context, there is mounting evidence for an association between psychiatric presentations and the expression variant connective tissue, commonly recognised as joint hypermobility. Joint hypermobility is common, frequently under-recognised, significantly impacts quality of life, and can exist in isolation or as the hallmark of hypermobility spectrum disorders (encompassing joint hypermobility syndrome and hypermobile Ehlers-Danlos syndrome). In this narrative review, we appraise the current evidence linking psychiatric disorders across the lifespan, beginning with the relatively well-established connection with anxiety, to hypermobility. We next consider emerging associations with affective illnesses, eating disorders, alongside less well researched links with personality disorders, substance misuse and psychosis. We then review related findings relevant to neurodevelopmental disorders and stress-sensitive medical conditions. With growing understanding of mind-body interactions, we discuss potential aetiopathogenetic contributions of dysautonomia, aberrant interoceptive processing, immune dysregulation and proprioceptive impairments in the context of psychosocial stressors and genetic predisposition. We examine clinical implications of these evolving findings, calling for increased awareness amongst healthcare professionals of the transdiagnostic nature of hypermobility and related disorders. A role for early screening and detection of hypermobility in those presenting with mental health and somatic symptoms is further highlighted, with a view to facilitate preventative approaches alongside longer-term holistic management strategies. Finally, suggestions are offered for directions of future scientific exploration which may be key to further delineating fundamental mind-body-brain interactions.

Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: United Kingdom

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 26, 2021
Peer-review started: February 26, 2021
First decision: April 20, 2021
Revised: May 12, 2021
Accepted: August 18, 2021
Article in press: August 18, 2021
Published online: October 19, 2021

P-Reviewer: Stoyanov D
S-Editor: Gong ZM
L-Editor: A
P-Editor: Ma YJ



Key Words: Joint hypermobility; Hypermobile Ehlers-Danlos syndrome; Psychopathology; Psychiatric disorders; Neurodevelopmental disorders; Mind-body relations

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Core tip: The association between vulnerability to psychological or psychiatric symptoms and hypermobile joints may initially appear counterintuitive to many clinicians. However, a relationship with anxiety is consistently confirmed across multiple studies worldwide. In this narrative review, we appraise increasing evidence linking neuropsychiatric presentations to hypermobility across the lifespan, including emerging links to neurodevelopmental disorders and stress-sensitive medical conditions. We discuss pertinent mechanistic insights in the context of growing understanding of mind-body interactions. We offer direction for future research and highlight implications for clinical practice, notably roles of timely screening and detection alongside longer-term holistic management strategies.

Citation: Sharp HEC, Critchley HD, Eccles JA. Connecting brain and body: Transdiagnostic relevance of connective tissue variants to neuropsychiatric symptom expression. *World J Psychiatr* 2021; 11(10): 805-820
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/805.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.805

INTRODUCTION

There is a rapidly growing body of evidence showing a curious excess of psychiatric burden among individuals with joint hypermobility. Common constitutional variants of connective tissue often present as joint hypermobility, reflecting increased laxity of ligaments and extended movement of joints beyond typically 'normal' limits (otherwise described as joint hyperlaxity, being double-jointed)[1]. Internationally, joint hypermobility is found in up to 20% of the general population, and is influenced by age, sex and ethnicity; hypermobility is more frequent in children, with higher prevalence in women, and Asian and African populations[2]. Hypermobility is also highly heritable, and has been proposed to be an autosomal dominant trait with incomplete penetrance, variable expressivity and influenced by sex[3]. The epidemiological characterisation is influenced by clinical definitions and assessment tools; the 9-point Beighton score is used most frequently to assess hypermobility in both clinical and research settings, although other methods include the Hospital del Mar criteria [4], and self-administered hypermobility questionnaires.

Hypermobility is a descriptive term and might exist as an asymptomatic and isolated feature. However, neuropsychiatric symptoms are among extra-articular manifestations that frequently accompany more widespread musculoskeletal symptoms that typically co-occur with hypermobility. In these cases, hypermobility appears as one feature of a multisystemic disorder[3]. This complexity is reflected in the current debate concerning terminology and classification: A consensus group in 2017 introduced the concept of hypermobility spectrum disorders (HSD); encompassing a continuum including hypermobile Ehlers-Danlos syndrome' (hEDS, previously EDS-HT), joint hypermobility syndrome [JHS, previously diagnosed according to the Brighton Criteria – Revised (1998)][5] and symptomatic hypermobility not fulfilling stricter criteria for other associated syndromes[6]. Diagnostic classification remains a contentious area, particularly since reliable genetic tests or physiological markers for HSD are presently lacking, so diagnosis relies solely on clinical criteria[6]. Hypermobility may also signal the presence of other heritable disorders of connective tissue including Marfan syndrome, osteogenesis imperfecta and Ehlers-Danlos syndromes which have a more clearly defined genetic basis[7]. Here, we review literature across a broad terminology referring to joint hypermobility and related syndromes.

Joint hypermobility is frequently under-recognised[3] and has a significant impact on quality of life across all age-groups[8,9]. Anxiety symptoms and disorders have a well-established link with hypermobility, yet growing evidence also now points

towards associations across psychiatric diagnoses, notably with affective illnesses, increasingly with neurodevelopmental disorders and with stress-sensitive medical conditions, including fibromyalgia, myelo-encephalomyelitis/chronic fatigue syndrome (ME/CFS) and irritable bowel syndrome (IBS). Awareness of these relationships are important to enhance understanding of early risk factors to allow screening and timely intervention for vulnerable individuals. The value of such a strategy is illustrated by a recent longitudinal study, which demonstrated that hypermobile children at age 14 years were more likely to suffer from anxiety and depression by age 18 years[10]. Increasing clinicians' awareness of the multisystemic features associated with hypermobility, especially psychiatric morbidity, will enable appropriate detection, diagnosis, and preventative intervention and can shape the implementation of effective longer-term holistic management strategies.

This paper presents a comprehensive narrative review of existent clinical knowledge and empirical evidence regarding the association of hypermobility with psychopathology. We also present a broad perspective on this expression of body-brain-mind interactions, including current mechanistic understanding, and we highlight implications for clinical practice and directions of future research.

LITERATURE SEARCH

This is a narrative review based on a comprehensive search of online databases (including MEDLINE, Embase and PsychInfo). Search terms included were 'hypermobility' and 'joint laxity' combined with each diagnostic category. This search comprised studies published from 1980 to 2021. Reference lists of identified papers were further scrutinised for additional relevant articles.

RESULTS

Anxiety

The expression of anxiety in the context of joint hypermobility was first recognised in the late 1980s. Subsequent research has repeatedly demonstrated this association, which has been the subject of several substantive reviews (for example[11]). Anxiety disorders are the most prevalent set of psychiatric illnesses[12], and hypermobility is most strongly linked to the expression of panic disorder and agoraphobia[13]. Moreover, state anxiety is a transdiagnostic symptom that is pervasive across distinct psychiatric disorders; even in non-clinical populations, hypermobility predicts elevated levels of trait and state anxiety, without necessarily reaching formal thresholds for anxiety disorder[14]. This pattern has been observed in the elderly[15] and in children, including both clinical[16,17] and non-clinical cohorts[18].

Affective disorders

Hypermobility is becoming a recognised vulnerability factor for affective disorders, particularly depression, especially if comorbid anxiety is present[19,20]. Patients with clinically significant hypermobility (*i.e.*, HSD/hEDS) demonstrate higher rates of depressive disorders (for example[21]), recently summarised in a meta-analysis[13] although there some inconsistencies within the literature[22]. A population-wide study, using Swedish national registries, observed a heightened risk of depression and increased rates of attempted suicide among hypermobile (EDS and HSD) individuals and their siblings[23]. Hypermobility is also associated with elevated self-report depressive symptoms in non-clinical populations[24]. There are a number of reasons why hypermobility may be linked to depression, and in many cases it is unclear whether studies have effectively controlled for anxiety, which could act as an explanatory mediator between hypermobility and depression, since these two conditions are highly comorbid. Other potential mediating factors common to both HSD/hEDS and depression include chronic pain, fatigue or impaired sleep[25].

An increased risk of bipolar affective disorder (BPAD) is also reported in individuals with ESD/HSD (relative risk, RR = 2.7)[23]. In this study, no difference in rates of schizophrenia were observed between people with and without hypermobility. Similarly, hypermobility is over-represented in patients with BPAD diagnosis attending a psychiatric outpatient setting[26]. However, further detailed studies are lacking, and the potential mediating role of other conditions, such as attention deficit hyperactivity disorder (ADHD; see below), are as yet unexplored.

Thus the link between hypermobility and BPAD remains preliminary.

Eating disorders

There are several case series and reports that describe the co-occurrence of EDS and eating disorders (reviewed in[27]). Elevated rates of hypermobility occur in both psychiatric outpatients with eating disorders[27] and in hospitalised in-patients with anorexia nervosa[28], who experienced excess gastrointestinal symptoms, orthostatic intolerance and fatigue (symptoms common to HSD/hEDS). A higher lifetime prevalence of eating disorder was also demonstrated in students with non-clinical hypermobility[29]. However, large and comprehensive epidemiological studies investigating this proposed link are lacking.

Mechanistically however, a proposed model of the relationship between eating disorders and HSD/hEDS recognises the contribution of both articular (such as temporo-mandibular disorders) and extra-articular features (including gastrointestinal problems, smell and taste abnormalities, dental problems, oral mucosal fragility) to difficult or painful eating, which reinforce dysregulated eating behaviour and associated weight loss[27,29]. Thus HSD/hEDS can plausibly contribute to, mask or even be misdiagnosed as an eating disorder.

Psychosis

The link between hypermobility and schizophrenia-type psychosis remains much less apparent than that seen in relation to anxiety, affective and eating disorders. One case-control study reported similar prevalence of HSD/hEDS in patients with schizophrenia and controls[30], a finding that was confirmed in a population matched cohort study[23]. Even in psychiatric outpatients, schizophrenia was reported to be negatively associated with hypermobility[26]. Nevertheless, hypermobility is implicated as a clinical marker for co-morbid anxiety in schizophrenia: Patients with comorbid hypermobility and schizophrenia express elevated rates of panic/agoraphobia disorder, exacerbating positive psychotic symptoms[31].

Personality disorder

Only one case-control study to date has investigated personality disorder in hypermobility, revealing elevated prevalence of personality disorder in JHS (RR = 5.8), especially of the obsessive-compulsive (anankastic) subtype[21]. It was speculated that that joint instability and associated imprecision of proprioception might underlie compensatory over-controlling behaviours (in the context of anxiety), and even that unrecognised JHS can contribute to perfectionism. However, rates of hypermobility were reported elsewhere to be no different in psychiatric outpatients with or without personality disorder[26]. While a number of possible putative mechanisms might link hypermobility to personality disorder (including anxious temperament and/or neurodevelopmental conditions including as ADHD), these findings should be interpreted cautiously, as there is an obvious need for large and well powered studies.

Addictions/substance misuse

Studies investigating addiction and substance misuse in the context of hypermobility are sparse. Early findings of elevated hypermobility scores in female chronic alcoholic patients[32] have not been replicated since. One longitudinal study revealed significantly higher prevalence of at-risk drinkers and smokers in young females with hypermobility compared to controls[33]. It is possible that alcohol and tobacco use could be overused to cope with chronic pain and anxiety (or indeed to self-medicate against ADHD symptoms, see below) and further studies should evaluate and control for these variables.

Neurodevelopmental disorders

In recent years, several authors have highlighted a relationship between hypermobility and neurodevelopmental disorders, notably autism (autistic spectrum disorders, ASD), ADHD and developmental coordination disorder (DCD)[34,35]. Interest in tic disorder (Tourette syndrome) and hypermobility is also growing. Hypermobility is frequently co-morbid with neurodevelopmental disorders and may contribute to the accompanying physical behavioural and cognitive symptoms that encompass motor difficulties, sleep and feeding problems, sensory hypersensitivities, behavioural hyperactivity, inattention, dysexecutive issues, speech and language problems and social deficits. Neurodevelopmental disorders most often present in school age children, and thus may precede or overshadow recognition of comorbid HSD/hEDS [35]. Nevertheless, these two clinical entities retain their association through into

adulthood[26,36]. Interestingly, however, subclinical expression of neurodevelopmental (ADHD, ASD or DCD) traits in the general population are not strongly associated with hypermobility, suggesting that the expression of this association is limited to clinical populations[37].

Autism: Evidence for an overlap between hypermobility and autism is growing. Initially described in case reports (reviewed in[38]), excess hypermobility has since been demonstrated in children with ASD (average age 4 years) in a case-control study [39], although differences in passive muscular tonicity may be a confound[40]. At a population-level, elevated rates of ASD is apparent in individuals with EDS/JHS and their siblings[23]. Both ASD and HSD/hEDS are considered heritable spectrum disorders that appear in infancy and share clinical presentations that include motor and coordination difficulties, sensory hypersensitivity/hyperalgesia, autonomic dysfunction, proprioceptive impairments and sleep disorders[34]. This has led to the suggestion that EDS/HSD might be considered as a subtype of ASD[34].

Furthermore, there has been longstanding recognition of the positive association between ASD and heritable disorders of connective tissue including Marfan's syndrome[41] and osteogenesis imperfecta[42]. ASD is known to be associated with several genetic causes, the most common being Fragile X syndrome (caused by mutations in *FMR1* gene). Up to half of patients with Fragile X syndrome are hypermobile. Soft skin, scoliosis and flat feet are common, providing further evidence for variant of collagen or related connective tissue[43]: The gene *FMR1* negatively regulates protein translation, which theoretically could cause downstream effects on collagen formation[43]. More broadly, across monogenic genetic syndromes strongly associated with both ASD and hypermobility, and known genetic causes of EDS subtypes, analyses of gene interactions reveal extensive gene clustering that might represent a biological mechanisms for the observed clinical overlap[34].

ADHD: Increasing clinical awareness of the co-occurrence of ADHD and hypermobility was confirmed by two case-control studies[44,45] and a population based cohort study[23], which also demonstrated higher rates of ADHD in siblings of children with HSD/hEDS diagnosis. Co-occurrence of ADHD and HSD/hEDS is also seen in adults[36,46].

DCD: According to DSM-5[47], EDS/JHS is included both as a differential diagnosis and as a potential comorbidity of DCD (previously termed developmental dyspraxia) in acknowledgement of the functional and clinical similarities[48]. High rates of symptoms related to HSD/hEDS are found among patients with DCD diagnosis, including pain and autonomic dysfunction, and there are significant commonalities in their motor features[48].

In children with HSD/hEDS diagnoses, high rates of clumsiness, impaired coordination and dyspraxia are observed[49], and up to 55% meet DCD criteria[50,51]. Similarly, 46%-64% of children with DCD are hypermobile[52,53], the exact figure depending on appropriate use of age appropriate Beighton score cut-offs[51].

Developmental tic disorder (Tourette syndrome): Despite emergent evidence describing hypermobility in ASD, ADHD and DCD, data concerning neurodevelopmental tic disorders (such as Tourette's syndrome) are remarkably lacking. To our knowledge, no current data have assessed this relationship in children. The first work in adults found elevated prevalence (38%) of hypermobility amongst 24 adults with Tourette syndrome[36]. Interestingly, these individuals had a high comorbidity of obsessive-compulsive disorder diagnoses (37.5%), another condition which is yet to be investigated with respect to hypermobility.

Stress medical sensitive conditions

Fibromyalgia and ME/CFS: Fibromyalgia and ME/CFS are both common overlapping disorders characterised by chronic pain, fatigue, sleep disturbance, cognitive complaints, gastrointestinal disturbance and affective problems.

There is further overlap of symptomatology and clinical findings with HSD/hEDS [54]. High rates of hypermobility are present in patients with fibromyalgia both as adults[55] and children[56], and in patients with ME/CFS, again both in adults[57] and children[58]. Hypermobility is specifically linked to the expression of pain and fatigue in these patients[59]. Conversely, the majority of EDS patients suffer from marked fatigue[60]. In fact, many patients with HSD/hEDS meet Fukada criteria for diagnosis of CFS[50], and hence it is argued that an assessment for hypermobility/variant connective tissues should be an integral part of a thorough evaluation of ME/CFS[61].

IBS and functional gastrointestinal disorders: Gastrointestinal symptoms (including nausea, abdominal pain, bloating, constipation and diarrhoea) are commonly experienced by patients with HSD/hEDS diagnosis[62]. Objectively, gastrointestinal dysmotility is observed[63] and is predicted by the symptoms and signs of dysautonomia, notably the occurrence of postural tachycardia syndrome (PoTS). Interestingly, psychiatric disorders, especially mood and somatoform disorders, occur at higher rates in patients with HSD/hEDS who experience gastrointestinal dysfunction and associated abdominal pain[64].

The prevalence of hypermobility appears to be greater in patients with IBS or gastrointestinal symptoms (especially functional dyspepsia) when compared to healthy controls[65]. This represents a subgroup (even variant phenotype) of patients who experience primary gastrointestinal problems with co-existing HSD/hEDS, who also demonstrate high comorbidity with chronic pain and fibromyalgia. These patients show increased somatisation score, urinary autonomic (symptom) score and reduced pain-related quality of life[66]. High rates of hypermobility are particularly observed in patients with constipation-predominant IBS[67], consistent with perturbation of colonic sensorimotor biomechanics consequent upon variant connective tissue.

However, while in adults the association between hypermobility and functional gastrointestinal disorders appears relatively robust, in children there is increasing evidence that the prevalence of hypermobility is similar for children with IBS, functional abdominal pain or functional constipation, and for healthy controls[68-70]. Intriguingly, this suggests that, in hypermobile individuals, IBS and functional GI symptoms may develop later in life perhaps interacting with hormonal or other maturational changes that impact connective tissue compliance.

Other associated stress-sensitive medical conditions: There are reports demonstrating that HSD/hEDS is also associated with increased risk of migraine (in females)[71], and with chronic regional pain syndrome[72], chronic myofascial pelvic pain[73], and stress incontinence[74].

DISCUSSION

The 'biopsychosocial approach' in psychiatry acknowledges the contribution of interconnected and interacting influences on the development and maintenance of psychiatric symptoms and diagnoses, including biological vulnerabilities, psychological factors and dynamic social context. The associations highlighted within this review, linking psychiatric symptoms and conditions to constitutional differences in connective tissue (apparent, in part, as joint hypermobility), likely depend on multiple mechanisms, which may differ between disorders. Hypothetically, joint hypermobility may represent a non-specific signature of a general mechanism linking variant connective tissue to psychological vulnerability, manifesting in a continuum across neurodevelopmental and psychiatric disorders. Alternatively, a pre-existing pathological process (as yet undiscovered) could predispose to both psychopathology and hypermobility in parallel *via* independent actions on the musculoskeletal and central nervous systems (Figure 1).

Psychosocial factors

Through lived experience, the presence of hypermobility from early childhood may directly underpin the development of psychiatric disorders. Excluding neurodevelopmental conditions, this makes temporal sense: The presence and consequences of hypermobility in childhood precedes the typically later emergence of psychiatric disorders in adolescence and adulthood. When symptomatic from a young age, the daily challenges of living with physical risks and difficulties associated with HDS/hEDS (including chronic pain and disability, threat of injury secondary to connective tissue fragility, restriction of social and physical activities and associated stigma) contribute to psychiatric vulnerability, avoidant behaviours and the development of anxiety and depressive symptoms[75].

Correspondingly, intense fear of pain and subsequent pain-avoidant strategies that limit movement (kinesiophobia) are common in HSD/hEDS[76]. These increase the likelihood of deconditioning and symptom progression, thereby furthering physical and psychological disability. In addition, problematic hypermobility is typically under-recognised and diagnostic delay is common[3]. Consequently, patients may experience frustration if their complaints are trivialised by healthcare professionals, adding to suffering and exclusion[75]. High anxiety and distress may drive

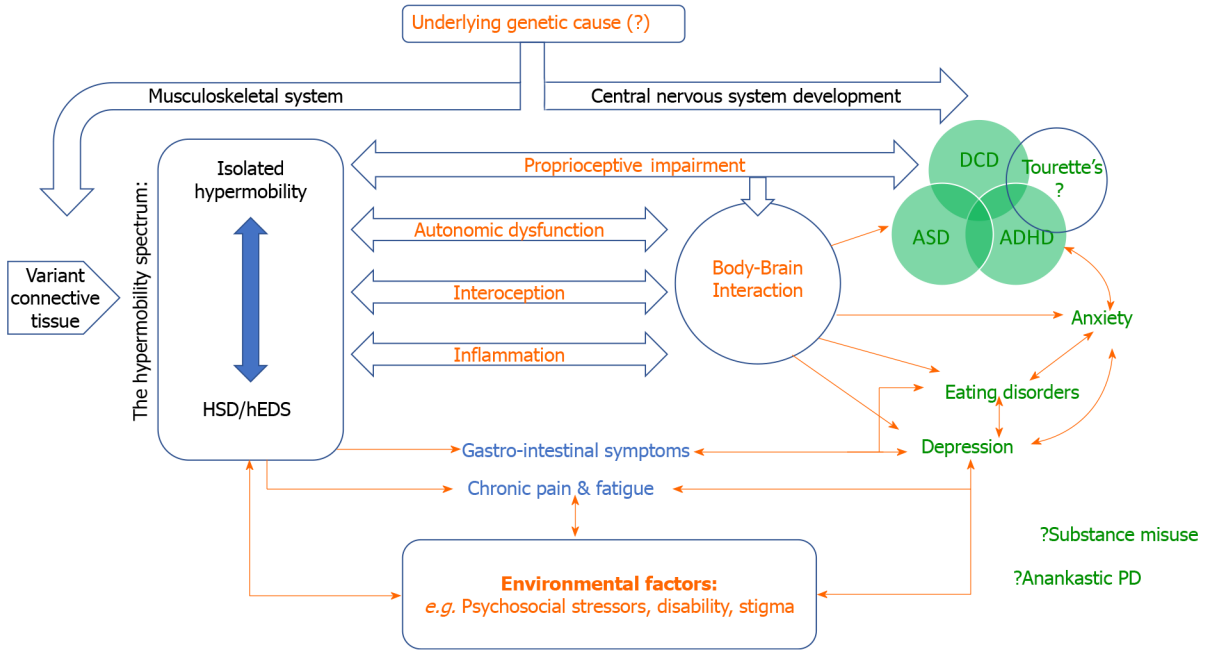


Figure 1 Diagram illustrating possible pathways for the aetiopathogenesis of psychiatric disorders in joint hypermobility. Orange text: Putative mechanisms; Blue text: Symptoms related to Hypermobility Spectrum Disorders/hypermobile Ehlers-Danlos Syndrome; Green text: Psychiatric and neurodevelopmental disorders. ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder; DCD: Developmental coordination disorder; PD: Personality disorder.

maladaptive behaviours including tobacco/alcohol use and disordered eating[33], and the psychosocial complexity surrounding hypermobility is associated with poorer quality of life in both adults[8] and children[9]. In hEDS patients, the psychological expression of high anxiety interacts with more severe fatigue and depressive symptoms, pain catastrophising, somatosensory amplification, to predict poorer social functioning and worse general health[20].

The bidirectional interaction between pain and psychological ill-health is widely recognised; chronic pain influences psychiatric symptoms including depression and anxiety, while low mood and negative emotions increase and maintain the experience of pain[77]. In this context, psychiatric disorders in HSD/hEDS may be secondary to pain symptoms rather than a primary or parallel manifestation. Hypermobility is a risk factor for chronic widespread pain[78], and hypermobile individuals exhibit sensory hypersensitivity to nociceptive stimuli[79] and secondary central sensitisation [80]. In fact, the presence of pain, rather than the degree hypermobility, is associated with the expression of psychiatric symptoms in EDS patients[81]. Similarly, the experience of pain and gastrointestinal dysfunction, rather than connective tissue features *per se*, is associated with higher rates of psychiatric disorders (especially mood and somatoform conditions) in HSD/hEDS patients[64].

Genetic factors

The relationship with pain is more nuanced; rates of psychiatric disorder are higher for HSD/hEDS than for other chronic pain conditions[13]. Thus, psychosocial theories fail to explain the full extent of all associations between hypermobility and psychopathological distress. This is particularly evident when considering neurodevelopmental disorders and in individuals with seemingly expressing sub-syndromic and isolated hypermobility. Instead, alternate theories propose that a common set of pathological mechanisms fundamentally predispose to the expression of both hypermobility and psychopathological symptoms (for example, as genetic pleiotropy).

There is interesting evidence from animals: Hypermobility is linked to exaggerated reactivity of behavioural/emotional arousal and excitability in dogs[82]. This finding suggests that the link between joint hypermobility and the affective control of bodily arousal is a universal transdiagnostic trait in mammals, influencing the expression of anxiety and behavioural responses. Moreover, such findings argue against conscious awareness and social implications of living with physical symptoms as a primary driver for the raised levels of psychopathology associated with hypermobility.

Genetic and/or early environmental influences are suggested by the increased risk of psychiatric disorders observed in the (unaffected) first-degree relatives of HSD/hEDS patients[23]. However, unlike other heritable disorders of connective tissue and EDS subtypes, genetic origins for HSD/hEDS remain poorly understood[3]. Previous identification of a genetic anomaly common to both anxiety and hypermobility, a duplication within chromosome 15, failed confirmation in subsequent studies[83]. A promising link has been noted between EDS and the gene TNXb (6p21.33), encoding the extracellular matrix glycoprotein *Tenascin-XB*, which is directly involved in connective tissue structure[84]. This molecule was recently identified as integral in enteric motor neurons and influencing nociceptive sensory neurons[85] and is expressed in the brain, suggesting further roles within the central nervous system. The extracellular matrix plays a critical role in both variant connective tissue and central nervous system development, and so alterations could predispose to abnormalities across central and peripheral systems[86].

Autonomic dysregulation and interoception

HSD/hEDS frequently co-occurs with autonomic dysfunction commonly experienced as symptoms of orthostatic intolerance and, in severe cases, PoTS[87]. The diagnosis of PoTS focuses on the characteristic elevation of heart rate during postural change and accompanying orthostatic intolerance[88]. The widespread presence of variant connective tissue is implicated as one potential physiological mechanism for the overlap between HSD/hEDS and dysautonomia. Within blood vessels, more compliant connective tissue may cause abnormal vascular reactivity, notably increased venous pooling on standing, which reduces venous return. Heart rate acceleration and a secondary hyperadrenergic state would thus result[87].

There is significant phenomenological overlap between symptoms of anxiety and panic and the symptoms of autonomic disfunction in orthostatic intolerance and PoTS: Physical symptoms include palpitations, breathlessness and dizziness[88], and these themselves could trigger and amplify anxiety states or be misperceived or diagnosed as panic attacks. Enhanced bodily awareness (described below) may be both a consequence and maintaining factor for such experiences, since altered autonomic reactivity will influence emotional state and vulnerability to psychiatric disorders[89]. Autonomic dysfunction is also demonstrable in children with neurodevelopmental conditions linked to hypermobility, notably ASD[90] and ADHD[91]. Again, there is symptomatic overlap between PoTS and ASD in both affective symptoms and sensory sensitivities[34]. The causal relationship between altered autonomic function and neurodevelopmental phenotypes remains unclear but evidence for an interactive association continues to grow.

Interoception refers to the afferent signalling to brain of changes in the internal physiological state of the body, and the perception of these changes. Interoceptive signals therefore represent the sensory limb of autonomic control loops (*e.g.*, the baroreflex), yet also reach perceptual awareness as physiological feelings including palpitations, nausea and arousal. In this way, interoceptive signals can guide motivation behaviour and are fundamental components of emotional feeling states. Central interoceptive representation and/or misinterpretation of dysregulated peripheral autonomic function may underpin the generation of a range of symptoms associated with hypermobility[92]. Dysregulated interoceptive processes are implicated in the expression of specific psychiatric symptoms, particularly anxiety [92]. Hypermobile individuals demonstrate enhanced subjective sensitivity to internal bodily sensations[93] and in more objective measures of detecting interoceptive signals. These differences are shown to mediate the relationship between state anxiety and hypermobility[94] and offer a potential treatment target for intervention.

Neuroimaging studies in hypermobile individuals reveal structural[93] and functional brain differences[94] notably within brain systems critical to emotional processing and anxiety[95], including regions such as insular cortex, that are also specifically implicated in interoceptive representation[94]. However, much of this work has been conducted in sub-clinical cohorts. While findings endorse a potential autonomic/interoceptive basis to vulnerability to anxiety and other neuropsychiatric symptoms, further work is needed to map these relationships in patients with psychiatric disorders in the context of hypermobility and to dissect levels of putative interoceptive dysfunction.

Immune dysregulation

Extensive bi-directional communication exists between the brain and the immune system and, increasingly, immune mechanisms are implicated in the pathogenesis of psychiatric disorders[96]. A specific association appears to exist between immune

system and hypermobility: Mast cell related disorders (giving allergy-like symptoms often across multiple organ systems) are commonly reported in patients with EDS/hEDS, highlighting a deep interrelationship between connective tissue and immune function occurring across genetic, molecular and physiological levels[97]. The concurrent expression of connective tissue impairments and immune dysfunction is speculated to influence vulnerability to psychiatric disorders. This may extend to neurodevelopmental disorders[34], as recent evidence highlights immune dysregulation in ASD[98].

Proprioceptive abnormalities

Abnormal proprioception is observed in both hypermobility and neurodevelopmental disorders and may account for their association[38]. Symptoms of both are present from early in childhood and appear highly heritable. Impaired proprioception particularly affects the lower limbs of children and adults with HSD/hEDS[99] and often leads to issues with coordination, balance, clumsiness and motor problems. Poor proprioception may directly account for the relationship between hypermobility and DCD[100]. Moreover, it is speculated that maintaining motor competences despite impaired proprioceptive function may overload executive functions and compete for attentional resources. This may in turn reinforce inattention in ADHD[101], and could further impact the timely acquisition of social and communication skills, thereby exacerbating ASD traits[34].

Implications for practice

We echo other authors calling for widened awareness of the diverse manifestations of hypermobility, particularly in psychiatry[34]. A recently proposed 'neuroconnective phenotype' model usefully describes the symptom profiles often expressed by people with hypermobility, including behavioural, psychopathological, somatic symptoms, somatosensory symptoms and somatic illness[11]. Considering the evidence presented here, we recommend vigilance for potentially overlooked mental health symptoms within the plethora of difficulties faced by patients living with HSD/hEDS. These should be part of a holistic clinical formulation that can enable appropriate psychoeducation, referral to mental health services, prompt diagnosis and access to optimal treatments.

Alongside this, we recommend screening for hypermobility, particularly in those presenting with neurodevelopmental disorders, but also in other mental health presentations, notably of panic and anxiety, in the context of physical symptoms, since articular and extra-articular features are often present[102] (Table 1). Simple screening using a 5-point questionnaire can detect hypermobility with high sensitivity and specificity[1] (Table 2). Early assessment can prompt referral to specialist services and thus reduce delayed or misdiagnosis of HSD/hEDS. It also widens opportunities for early intervention to prevent progression of psychological as well as physical symptoms throughout the lifespan.

Currently, there no specific guidelines for the psychological or pharmacological management of psychiatric conditions in patients with HSD/hEDS. Nevertheless, considering the complex difficulties faced by these patients, we recommend multidisciplinary management across mental and physical health professionals, including early involvement of physiotherapy to facilitate improvement of proprioception and bodily awareness[19].

Limitations

One considerable limitation in evaluating the growing evidence base describing the association between joint hypermobility and psychiatric disorder is the variable use of assessment tools to measure hypermobility. Specific genetic tests or biomarkers do not exist. The use of assorted self-report questionnaires and distinct clinical assessment scales is liable to subjective interpretation and observer dependence, limiting reliability. Furthermore, the application of age-dependent cut-off scores remains controversial. Our review has considered articles covering the whole spectrum of hypermobility and related disorders yet highlights the need for further disentangling research.

Nevertheless, individuals with higher anxiety and more severe symptoms are more likely to seek medical attention, join patient support associations and participate in research studies, even among 'non-clinical' populations. Those recruited may be experiencing higher distress, and hence introduce sampling bias. Published studies may therefore overlook (and over-pathologise) the spectrum of hypermobility presentations.

Table 1 Indications prompting screening for hypermobility spectrum disorders/hypermobile Ehlers-Danlos syndrome amongst patients presenting to mental health services (adapted from Ross and Grahame 2011[102])

	Extra-articular features	Articular features
In children and adolescents	Prolonged fatigue or tiring easily	Joint dislocations/subluxations (including congenital hip dislocation)
	Poor motor coordination or 'clumsiness' (such as poor ball catching and poor handwriting)	Recurrent ankle sprains
	Chronic widespread pain or 'growing pains'	
	Delayed walking, with bottom shuffling instead of crawling	
In adults	Prolonged unexplained fatigue (including ME/CFS)	Recurrent joint dislocations
	Chronic widespread pain, particularly if unresponsive to analgesia (including fibromyalgia)	Multiple soft tissue injuries/rheumatisms
	Functional gastrointestinal disorders (such as IBS, functional dyspepsia, constipation)	Premature osteoarthritis
	Autonomic dysfunction (such as orthostatic intolerance or PoTS)	Persistent or recurrent joint pains
	Progressive loss of mobility secondary to pain or pain-avoidance strategies	
	Laxity in supporting tissues (such as hernias, varicose veins, pelvic floor dysfunction)	
	Soft/hyperextensible skin, unexplained striae, easy bruising	

ME/CFS: Myelo-encephalomyelitis/chronic fatigue syndrome; IBS: Irritable bowels syndrome; PoTS: Postural tachycardia syndrome.

Table 2 Five-point screening questionnaire for detecting hypermobility (from Hakim and Grahame 2003[1])

1 Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2 Can you now (or could you ever) bend your thumb to touch your forearm?
3 As a child, did you amuse your friends by contorting your body into strange shapes OR could you do the splits?
4 As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5 Do you consider yourself 'double-jointed'?
Answering yes to two or more questions suggests hypermobility with sensitivity 80%-85% and specificity 80%-90%

Future research

There is strong evidence linking the expression of mental health disorders to hypermobility as a signature of variant connective tissue. However, future research is needed to investigate the genetic, neural and psychophysiological mechanisms for such mind-body interactions. Longitudinal studies are needed to better identify which hypermobility individuals develop psychiatric symptoms or diagnoses to delineate contributions of precipitating, perpetuating, and preventative factors and map how these progress with time. Such fresh insights offer the potential for the implementation of early preventative strategies in at-risk individuals, minimising complications in later life.

We argue that variant connective tissue contributes to the pathogenesis of mental health disorders: This likely represents an 'endophenotype'; a measurable component along the pathway between phenotype and disease, an important emerging concept in neuropsychiatric research[103]. In this respect, hypermobility is clearly heritable, and presents with excess relative risk in relatives[23]. In addition, its role has biological plausibility, is not state dependent, and is easily testable. However, there remains much to understand, not least how hypermobility is connected with candidate genes. In this context, across psychiatric disorders the presence of hypermobility could represent a phenotypic subgroup of patients[103]. Hypermobility may also act as a clinical marker for specific target symptoms *e.g.*, anxiety[16], as demonstrated in hypermobile patients with schizophrenia[31] or for sensory hypersensitivities, *e.g.*, to olfactory stimuli in patients with panic disorder[104].

More research is also needed to determine if this patient subset responds differently to treatment, allowing for a 'personalised medicine' approach. For example, a dietary intervention (low FODMAP) for irritable bowel syndrome is reportedly more effective in hypermobile compared to non-hypermobile patients[105]. Dysfunctional coping strategies are associated with hypermobility[33], so psychological approaches addressing these could prove beneficial. Anecdotally, sensitivity to unwanted drug side-effects is high in this group. The first randomised controlled trial of a targeted non-pharmacological therapy for anxiety in the context of hypermobility is currently ongoing, comparing modified interoceptive training to standard supportive treatment in individuals with hypermobility and anxiety[106].

CONCLUSION

In conclusion, alongside the well-known link between hypermobility and anxiety, recognition of which has expanded across age groups, there is growing evidence of associations with depression, eating disorders, neurodevelopmental conditions and stress-sensitive medical conditions. There remains a paucity of evidence for links with schizophrenia and addictions. We recommend clinicians across different specialities are aware of the transdiagnostic nature of HSD/hEDS, which may present with both primary and secondary difficulties in psychological and physical domains. In particular, professionals encountering patients with mental health difficulties should consider the prospect of underlying hypermobility as a potential influence on neuropsychiatric symptom progression in this subgroup of patients.

While hypermobility and psychopathological attributes are conventionally considered distinct, their association affirms the pervasive interplay of mind, brain and body. Perceptions, emotions, cognitions and behaviours are dynamically coupled to the state of the body through both unconscious and conscious mechanisms[89]. Further investigation of the psychophysiological, cellular, molecular and genetic underpinnings of the link between hypermobility and psychiatric disorders may provide clinically relevant insights to improve recognition, identify treatment targets, and plan holistic management strategies across the lifespan that combine both psychiatric and somatic approaches.

ACKNOWLEDGEMENTS

We wish to thank Professor Rodney Grahame, Professor Christopher Mathias, Dr. Valeria Iodice, Professor Antonio Bulbena and Dr. Baeza-Velasco for their inspiration for this paper. We are also grateful to the journal's editors and to Rosie Mulgrue for proof-reading input.

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World J Psychiatr 2021 October 19; 11(10): 821-829

DOI: 10.5498/wjp.v11.i10.821

ISSN 2220-3206 (online)

MINIREVIEWS

Psychiatric sequelae in COVID-19 survivors: A narrative review

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Author contributions: All authors contributed to the concept of this study; Putri C, Arisa J, and Hananto JE designed the study; Hariyanto TI and Kurniawan A analyzed the data and wrote the manuscript; Putri C, Arisa J, and Hananto JE approved the final manuscript; All authors reviewed and approved the final draft.

Conflict-of-interest statement: The authors declare that they have no competing interests to disclose.

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Manuscript source: Invited

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Abstract

In December 2019, a novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was initially reported in Wuhan, China. Previous epidemics including SARS and middle east respiratory syndrome raises concern that COVID-19 infection may pose a significant threat to the mental health of affected individuals. Studies and reviews have shown the acute psychiatric manifestations in COVID-19 patients, although long term psychiatric sequelae are predicted, there are only few review studies about the long term psychiatry outcome in COVID-19 survivors. Clinically significant post-traumatic stress disorder, anxiety, and/or depression among COVID-19 survivors during 14-90 d were observed following the diagnosis. Risk of anxiety or depression were higher in patients with more severe illness at 6 mo follow-up, early convalescence, and at 1 mo follow-up. Diagnosis of COVID-19 Led to more first diagnoses and relapses of psychiatric illness during the first 14-90 d after COVID-19 diagnosis. The possible underlying mechanisms of psychiatric sequelae in COVID-19 infection are neurotropism, immune response to SARS-CoV-2, hypothalamo-pituitary-adrenal axis hyperactivity, disrupted neuronal circuits in several brain regions, increased stress levels, neuroinflammation, and neuronal death. This study will review the psychiatric sequelae in previous coronavirus pandemics, current studies, risk factors, and thorough explanation on patho-physiology of the psychiatric sequalae in COVID-19 survivors.

Key Words: Psychiatrics sequelae; Mental disorders; COVID-19; SARS-CoV-2

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manuscript

Specialty type: Psychiatry

Country/Territory of origin: Indonesia

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 26, 2021
Peer-review started: February 26, 2021
First decision: May 5, 2021
Revised: May 13, 2021
Accepted: August 18, 2021
Article in press: August 18, 2021
Published online: October 19, 2021

P-Reviewer: Wang MK
S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Wang LYT

Core Tip: Studies and reviews have shown the acute psychiatric manifestations in coronavirus disease 2019 (COVID-19) patients, and although long term psychiatric sequelae are predicted, there are only few review studies about the long-term psychiatry outcome in COVID-19 survivors. Clinically significant post-traumatic stress disorder, anxiety, and/or depression among COVID-19 survivors during 14-90 d following the diagnosis. Risk of anxiety or depression were higher in patients with more severe illness at 6 mo follow-up, early convalescence, and at 1 mo follow-up. Diagnosis of COVID-19 Led to more first diagnoses and relapses of psychiatric illness during the first 14-90 d after COVID-19 diagnosis.

Citation: Putri C, Arisa J, Hananto JE, Hariyanto TI, Kurniawan A. Psychiatric sequelae in COVID-19 survivors: A narrative review. *World J Psychiatr* 2021; 11(10): 821-829
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/821.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.821

INTRODUCTION

In December 2019, a novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was initially reported in Wuhan, China. This disease has caused a national outbreak of severe pneumonia in China and spread worldwide rapidly. On January 30th, 2020, the World Health Organization (WHO) declared the outbreak to be a Public Health Emergency of International Concern[1]. As of February 5th, 2021, there have been 103989900 confirmed cases of COVID-19, including 2260259 deaths, globally[2]. Previous published meta-analysis studies have identified several comorbidities[3-7], home medications[8,9], and laboratory values[10,11] which are associated with severe outcomes and the risk of dying from COVID-19.

Based on previous epidemics experiences, including SARS and middle east respiratory syndrome (MERS), it is recognized that COVID-19 infection may pose a significant threat to the mental health of affected individuals[12]. Studies have reported psychiatric symptoms in SARS survivors, including post-traumatic stress disorder (PTSD), depression, panic disorder, and obsessive-compulsive disorder at 1 to 50 mo follow up[13-15].

Previously published systematic review and meta-analysis studies have shown that the prevalence of psychological consequences of those inflicted or suspected of COVID-19, health care workers, and the general population is 26% (95%CI: 21-32). Pooled prevalence for symptoms of PTSD was 33% (0–86), anxiety 28% (21-36), stress 27% (14-43), and depression 22% (13-33)[16]. Although psychiatric sequelae are predicted, there are only a few studies about the long-term psychiatry outcome in COVID-19 survivors.

The pandemic itself is a significant psychological stressor in addition to its enormous impact on social and economic sectors worldwide. Isolation and small social networks during quarantine period limit access to external supports[17].

Beside the pandemic-associated psychological distress, there are several arguments that may explain the association between COVID-19 and psychological symptoms as its sequelae. Hereby, we review the current evidence regarding the characteristics of psychiatric sequelae from COVID-19 and the mechanism of how COVID-19 infection affects the communication between endocrine, immune, and central nervous systems, resulting in psychiatric sequelae in COVID-19 survivors (Figure 1).

PSYCHIATRIC SEQUELAE IN PREVOUS CORONAVIRUS PANDEMICS

Past pandemics have demonstrated that diverse types of neuropsychiatric symptoms, such as encephalopathy, mood changes, psychosis, neuromuscular dysfunction, or demyelinating processes, may accompany acute viral infection, or may follow infection by weeks, months, or longer in recovered patients[18].

A meta-analysis study conducted by Rogers *et al*[19] showed that the prevalence of PTSD in the post-illness stage among patients admitted to hospital for SARS or MERS

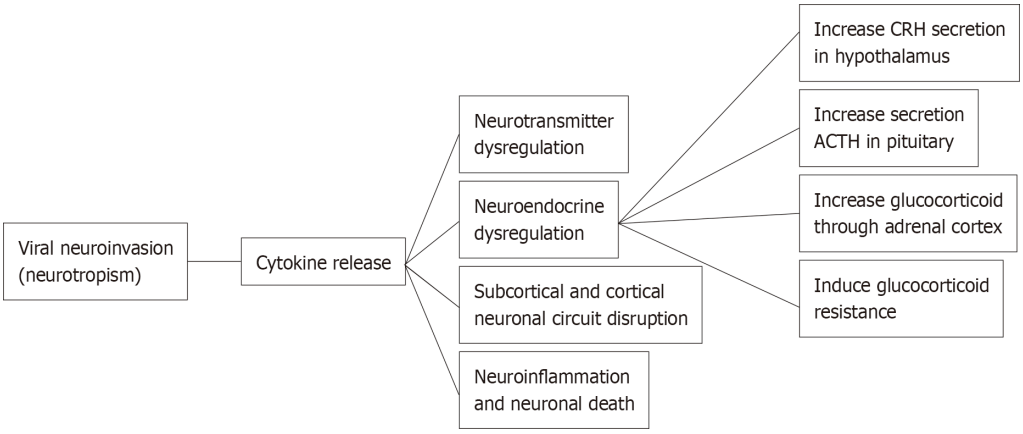


Figure 1 Mechanisms of psychiatric sequelae in coronavirus disease 2019 survivors. ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone.

was 32.2% (95%CI 23.7–42.0; 121 of 402 cases from 4 studies), while the prevalence of depression was 14.9% (12.1–18.2; 77 of 517 cases from 5 studies), and that of anxiety disorders was 14.8% (11.1–19.4; 42 of 284 cases from 3 studies). 446 (76.9%; 95%CI 68.1–84.6) of 580 patients from 6 studies had returned to work at a mean follow-up time of 35.3 mo (SD 40.1).

Survivors of SARS-CoV-1 were clinically diagnosed with PTSD (54.5%), depression (39%), pain disorder (36.4%), panic disorder (32.5%), and obsessive compulsive disorder (15.6%) at 31 to 50 mo post-infection, a dramatic increase from their pre-infection prevalence of any psychiatric diagnoses which is only 3%[15]. Fatigue, myalgia, depression and poor sleep were seen in a cohort of 22 patients and a post-SARS syndrome, similar to fibromyalgia or post viral chronic fatigue syndrome, was suggested, possibly as a result of the psychological trauma or neurological involvement of SARS[20]. SARS has been since described as a mental health catastrophe as a result of the psychological impact on survivors, especially in Health Care Workers, including anxiety, depression, psychosis and high rates of PTSD[21]. After a mean post-SARS duration of 39 mo, 181 subjects underwent interviews with SCID-II for assessment of any psychiatric morbidity. The commonest disorders were major depressive disorder, post-traumatic stress disorder, somatoform pain disorder, and panic disorder[22].

One study showed that at 12 mo post-MERS 27% of survivors had depression and 42% had PTSD, which improved at 18 mo but was still a problem in 17% and 27% of survivors respectively[23]. At 4-6 mo after release from isolation, anxiety symptoms were observed in 3.0% (95%CI: 2.2%-3.9%). Feelings of anger were present in 6.4% (95%CI: 5.2%-7.6%)[24].

Severance *et al*[25] also found the increased prevalence of antibodies against 4 HCoV strains in patients with a recent psychotic episode compared to non-psychiatric controls, suggesting a possible relationship between CoV infections and psychosis, which may also occur in SARS-CoV-2. Seropositivity for coronaviruses associated with suicide and psychosis persisting 1 year after SARS[26].

CURRENT STUDIES ON PSYCHIATRIC SEQUELAE IN COVID-19 SURVIVORS

Recent ambi-directional cohort study of 1733 of COVID-19 survivors in Wuhan found that risk of anxiety or depression were higher in patients with more severe illness at 6 mo follow-up. Patients showed an odds ratio OR 0.88 (0.66–1.17; $P = 0.37$) for scale 4 (requiring supplemental oxygen) *vs* scale 3 (not requiring supplemental oxygen) and OR 1.77 (1.05–2.97; $P < 0.05$) for scale 5–6 (requiring HFNC, NIV, or IMV) *vs* scale 3 for anxiety or depression. Sleep difficulties (26%, 437 of 1655) were one of the most common symptoms reported[27].

Current studies reported clinically significant PTSD, anxiety, and/or depression among COVID-19 survivors during 14-90 d were observed following the diagnosis[28-32], early convalescence[33], and at 1 mo follow-up[34]. PTSD was the most common condition reported, with female gender, past traumatic events, protracted symptoms,

stigmatization, and a negative view on the COVID-19 pandemic as the predictors of symptoms severity ($P < 0.05$)[28]. Older survivors experienced less severe PTSD and anxiety symptoms than younger ones ($P = 0.04$ and $P = 0.045$, respectively). Older age had a significant inverse association with the severity of emotional symptoms of depression ($P < 0.001$)[33].

One retrospective case control cohort studies of 62354 COVID-19 cases in the USA found that diagnosis of COVID-19 Led to more first diagnoses and relapses of psychiatric illness during the first 14-90 d after COVID-19 diagnosis compared control health events (HRs between 1.58 and 2.24, all $P < 0.0001$). At 90 d, the estimated probability of having newly diagnosed psychiatric illness after COVID-19 diagnosis was 5.8% (95%CI: 5.2-6.4) compared with 2.5%-3.4% of patients in the comparison cohorts. The most frequent psychiatric diagnosis was anxiety disorder (HRs 1.59–2.62, all $P < 0.0001$). The probability of a first diagnosis of mood and psychotic disorder was 2% (95%CI: 1.7-2.4) and 0.1% (95%CI: 0.08-0.2), respectively. The rate of first or relapsed psychotic disorder diagnosis after COVID-19 diagnosis was 0.9% (95%CI: 0.8-1.1). The probability of a first diagnosis of insomnia was 1.9% (95%CI: 1.6-2.2; HRs 1.85-3.29, all $P < 0.0001$). The probability of being diagnosed with dementia was increased after a diagnosis of COVID-19 among patients older than 65 years the risk was 1.6% (95%CI 1.2-2.1; HRs 1.89-3.18). COVID-19 patients admitted to hospital have higher risk of psychiatric sequelae than patients not requiring admission (HR 1.40, 95%CI: 1.06-1.85; $P = 0.019$)[30].

RISK FACTORS

Psychiatric outcomes of COVID-19 patients are affected by several biological factors (*e.g.*, obese, older age, pregnancy) and external psychosocial stressors (*e.g.*, social isolation, financial stress). Associated with systemic inflammation and impaired immunity, obesity not only can increase vulnerability for COVID-19 infection, but also constitutes an important risk factor for the development or worsening of psychiatric disorders[32].

Aging is related to cytokine imbalances, which are high levels of pro-inflammatory cytokines, low levels of anti-inflammatory cytokines and decrease in T-cell-mediated function[33]. These changes in elderly may be associated with higher susceptibility to viral diseases and neuropsychiatric disturbances, such as cognitive impairments[34].

Female COVID-19 survivors are at higher risk for developing psychiatric symptoms [27,30,31]. Maternal immune activation in early stages of fetus development is another important risk factor for developing neuropsychiatric disturbances, such as autism spectrum disorder[35]. The presence of family members or close relatives infected was significantly related to anxiety and depression ($P < 0.001$)[30]. Patients with a positive previous psychiatric diagnosis showed a significant increase in psychiatric symptoms measures[29,31].

Recent studies among COVID-19 patients found greater occurrence of depressive and anxiety disorders in people who are in quarantine, front-line workers or among family members of affected patients[36]. This finding suggested psychological stressors, such as social isolation, psychological impact of a severe and potentially fatal illness, concerns about infecting others, and stigma can lead to psychological consequences[31,36]. Loneliness has been associated with several psychiatric disorders, such as depression, anxiety, and suicide behavior[37]. In addition, it has been shown that lonely people present several immune dysregulations, such as upregulated expression of pro-inflammatory cytokine genes[38]. Studies with animal models have provided important clues on the neurobiological and the behavioral consequences of social isolation. In rodents, the stress of social isolation leads to changes in several neurotransmitter systems (*e.g.*, dopaminergic, adrenergic, serotonergic, gabaergic, glutamatergic, nitrergic, and opioid systems). The social isolation stress can also lead to hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis through an increase in corticosterone production and release in rodents [39].

Financial problems may enhance the impact of social isolation on mental health during quarantine[40]. Studies showed that a worse socioeconomic status is directly related to higher systemic levels of inflammatory markers such as interleukin (IL)-6 and C-reactive protein[41].

PATHOPHYSIOLOGY

The underlying mechanisms of psychiatric sequelae in COVID-19 infection are still unknown and in need further investigation. However, the relationship between COVID-19 severity and psychiatric outcome, albeit modest, might represent a dose-response relationship, suggesting that the association might be mediated by biological factors directly related to the virus (*e.g.*, immune system, viral load)[29] (Figure 1 and Table 1).

Neurotropism

Coronaviruses, including SARS-CoV-2 also invade the central nervous system. There is evidence of SARS-CoV-2 neurotropism based on clinical, pathological, and molecular studies. SARS-CoV-2 invades epithelial cells by binding to ACE2 on the cell membrane which is also expressed in the brain, both in neurons and glia. There are several routes for viral neuroinvasion, including trans-synaptic transfer across infected neurons in splanchnic nerves, entry *via* the olfactory nerve, infection of vascular endothelium, leukocyte migration across the blood-brain barrier (BBB), and/or a conjunctival route[42].

Immune response to SARS-CoV-2

COVID-19 infection triggers a local immune response, recruiting macrophages and monocytes that release cytokines and induce T and B cell responses. In most people, this adaptive immune response is capable of resolving the infection. However, in some individuals, a dysfunctional immune response occurs which may cause severe lung damage and multiple organ failure through catalyzing enzymes such as proteases and toxic free radicals. These processes may damage immune residue in brain neural circuits among COVID-19 patients[43].

High levels of IL-1β, IL-6, interferon-γ, CXCL10, and CCL2 were observed in COVID-19 patients, suggesting an activation of T-helper-1 cell function. Moreover, unlike in SARS and MERS, elevated levels of T-helper-2 cell-secreted cytokines (such as IL-4 and IL-10) were found in COVID-19 patients[44]. Persistent with these findings, emerging evidence found that COVID-19 infection can induce a cytokine release syndrome as a part of host's innate immune, commonly observed in cytopathic virus infections[45]. Soluble cytokines that reach the brain have significant effects on multiple neurotransmitters, including dopamine, serotonin, norepinephrine and glutamate through impact on their synthesis, release, and reuptake[46]. Changes in the metabolism of neurotransmitters contributed to the pathophysiology of various psychiatric disorders, such as depression, anxiety, and PTSD[47,48]. Pro-inflammatory cytokines increase oxidative stress which damages cellular membranes and reduce the expression of excitatory amino acid transporters that are necessary to end glutamatergic signaling that results in elevated glutamate levels[42]. Hence, the immune activation hypothesis which has been postulated for many psychiatric disorders may be a relevant mechanism for mental health issues in COVID-19 survivors[18] (Figure 1).

HPA axis hyperactivity

Since communication occurs between the endocrine, immune, and central nervous system, the activation of inflammatory responses may affect neuroendocrine processes, and vice versa. During COVID-19 infection, pro-inflammatory cytokines are released by immune cells present in the periphery (*e.g.*, macrophages, T and NK cells) and/or in the brain (microglia). High levels cytokines can affect neuroendocrine axis and activate the HPA axis at three different levels: increasing the secretion of the corticotropin-releasing hormone in the hypothalamus, the secretion of adrenocorticotropic hormone in the pituitary, and release of glucocorticoids (*e.g.*, cortisol) through the adrenal cortex[49]. Inflammatory cytokines and their signaling pathways including MAPK, NF-kappa B, signal transducers and activators of transcription and cyclooxygenase have been found to inhibit glucocorticoid receptor (GR) function by acting on its translocation or on GR-mediated gene transcription, thus inducing glucocorticoid resistance that results in dysfunction in the negative feedback between the HPA axis and the immune system.

HPA axis hyperactivity is one of the characteristic features of major depression (MD). Some studies have suggested that glucocorticoids also contribute to the hippocampal atrophy found in patients with MD[50]. Rates of insomnia diagnosis were also markedly elevated, in agreement with predictions that circadian disturbances will follow COVID-19 infection. The HPA axis plays important roles in modulating sleep. Therefore, dysregulation of the HPA axis at any level can disrupt

Table 1 Comparison of psychiatric sequelae in severe acute respiratory syndrome, middle east respiratory syndrome, and coronavirus disease 2019 survivors

Psychiatric sequelae	SARS	MERS	COVID-19	Ref.
Post-traumatic stress disorder	√	√	√	[15,21-23,28,29]
Pain disorder	√	-	-	[15,21]
Panic disorder	√	√	√	[15,21,22,24,27-29]
Depression	√	√	√	[20-23,27-29]
Sleep problems	√	-	√	[20,27,29]
Psychosis	√	-	-	[21]
Dementia	-	-	√	[29]

COVID-19: Coronavirus disease 2019; MERS: Middle east respiratory syndrome; SARS: Severe acute respiratory syndrome.

sleep[51].

Disrupted neuronal circuits in several brain regions

Findings from neuroimaging studies indicate that inflammatory cytokines impact the function of subcortical and cortical neuronal circuits in the brain, especially the basal ganglia and dorsal anterior cingulate cortex, leading to significant changes in motor activity and motivation as well as anxiety, arousal and alarm. Chronic activation of this innate behavioral and immune response may contribute to the development of depression and anxiety disorders in vulnerable individuals. Other brain regions including amygdala, hippocampus, insula, dorsolateral prefrontal cortex and subgenual anterior cingulate cortex are also involved[46].

Increased stress levels

Increased stress levels and worries during pandemic are also the major contributing factors to clinical insomnia[52]. Worry provokes cognitive arousal and may therefore disturb sleep cycle. Reduced physical fatigue and exposure to the sun, as well as increased use of electronic devices may also affect sleep homeostasis. A study showed increased prevalence of insomnia in women compared with men, suggesting that they are more prone to develop stress-related disorders such as post-traumatic stress disorder and anxiety disorders[53]. Sleep disturbances are involved in PTSD development and maintenance[54].

Neuroinflammation and neuronal death

SARS-CoV-2 infection triggers a massive release of inflammation signals leading to BBB dysfunction, injury to astrocytes, activation of microglia and astrocytes resulting in neuroinflammation and neuronal death. Immune response and excessive inflammation in COVID-19 may also speed up the progression of brain inflammatory neurodegeneration. An early report found that one in three individuals with COVID-19 had dysexecutive syndrome at the time of hospital discharge. SARS-CoV-2 can infect endothelial cells leading to further damage of the vasculatures. The resulting hypoperfusion may disrupt energy substrates needed for maintaining neuronal networks thereby accelerating cognitive decline. Damage to limbic and cortical regions could cause retrograde and anterograde amnesia[42].

CONCLUSION

Studies above identified COVID-19 survivors at high risk for psychological problems. Good social support and a number of simple attitudes or activities should be done to prevent psychiatric sequelae in COVID-19 survivors, such as strengthen bonds with other people through social media, think and talk positively, sleep properly, balance diet, regular daily routine, relaxation exercise and other healthy lifestyle measures[49,55]. Music therapy can also be a relevant and simple strategy to improve mental health. A meta-analysis study showed music can modulate cytokine levels (including reducing IL-6 levels), as well as neuroendocrine-immune responses triggered by

physical stress caused by viral infection[56]. In addition, music interferes positively in the immune system when subjected to acute stress, regulating the function of IL-6 and the HPA axis[57]. On the other hand, substance use, eating too much fast food, excessive online activity, excessive watching television, and trusting fake news should be avoided[58].

We suggested that all COVID-19 survivors should be screened for stress disorder, anxiety, and depression regularly to identify those with psychological distress for timely intervention; particularly those with the positive predictive factors (female, prior psychiatric diagnosis, presence of infected family members). Previous studies found that psychiatric sequelae occurred months after the acute infection, therefore the need for sustained follow-up beyond documenting acute stress levels, is important and urgent. Strategies aiming at minimizing mental problems during not only the acute phase of infection but also recovery phase must be designed. Since poorer mental health can be associated with shorter life expectancy and higher economic burden, political and health authorities should be aware of the mental health of COVID-19 survivors[59-61].

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World Journal of Psychiatry

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World J Psychiatr 2021 October 19; 11(10): 830-840

DOI: 10.5498/wjp.v11.i10.830

ISSN 2220-3206 (online)

MINIREVIEWS

Metabotropic glutamate receptors and nitric oxide in dopaminergic neurotoxicity

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Author contributions: Bashkatova V wrote the paper.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Manuscript source: Invited manuscript

Specialty type: Neurosciences

Country/Territory of origin: Russia

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0

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Abstract

Dopaminergic neurotoxicity is characterized by damage and death of dopaminergic neurons. Parkinson's disease (PD) is a neurodegenerative disorder that primarily involves the loss of dopaminergic neurons in the substantia nigra. Therefore, the study of the mechanisms, as well as the search for new targets for the prevention and treatment of neurodegenerative diseases, is an important focus of modern neuroscience. PD is primarily caused by dysfunction of dopaminergic neurons; however, other neurotransmitter systems are also involved. Research reports have indicated that the glutamatergic system is involved in different pathological conditions, including dopaminergic neurotoxicity. Over the last two decades, the important functional interplay between dopaminergic and glutamatergic systems has stimulated interest in the possible role of metabotropic glutamate receptors (mGluRs) in the development of extrapyramidal disorders. However, the specific mechanisms driving these processes are presently unclear. The participation of the universal neuronal messenger nitric oxide (NO) in the mechanisms of dopaminergic neurotoxicity has attracted increased attention. The current paper aims to review the involvement of mGluRs and the contribution of NO to dopaminergic neurotoxicity. More precisely, we focused on studies conducted on the rotenone-induced PD model. This review is also an outline of our own results obtained using the method of electron paramagnetic resonance, which allows quantitation of NO radicals in brain structures.

Key Words: Dopaminergic neurotoxicity; Metabotropic glutamate receptors; Nitric oxide; Rotenone; Parkinson's disease

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Core Tip: Dopaminergic neurotoxicity is characterized by damage and death of

Grade D (Fair): 0
Grade E (Poor): 0

Received: February 28, 2021
Peer-review started: February 28, 2021
First decision: March 30, 2021
Revised: April 11, 2021
Accepted: August 3, 2021
Article in press: August 3, 2021
Published online: October 19, 2021

P-Reviewer: Xu WX
S-Editor: Zhang H
L-Editor: A
P-Editor: Wang LYT



dopaminergic neurons. Chronic systemic exposure to rotenone (an inhibitor of mitochondrial complex I and a commonly used pesticide) induced dopaminergic degeneration and reproduced many features of human Parkinson's disease in rats. The current paper aims to review the involvement of metabotropic glutamate receptors and the contribution nitric oxide to dopaminergic neurotoxicity.

Citation: Bashkatova V. Metabotropic glutamate receptors and nitric oxide in dopaminergic neurotoxicity. *World J Psychiatr* 2021; 11(10): 830-840
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/830.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.830

INTRODUCTION

The dopaminergic system is a part of the brain that plays a key role in the control of locomotor activity, stress reactions, aggressive behavior, and mechanisms of the formation of dependence in humans and animals[1,2]. Dopaminergic neurotoxicity is characterized by damage and death of dopaminergic neurons. The contribution of dopaminergic neurotoxicity to the pathogenesis of several disorders of the central nervous system (CNS), such as Parkinson's disease (PD)[3,4], Tourette syndrome[5], drug abuse[6,7], and schizophrenia[8,9], has been postulated. Currently, neurodegenerative diseases are a major cause of disability around the world. PD is the second-leading cause of neurodegenerative disorder after Alzheimer's disease (AD)[4]. PD is manifested primarily by movement disturbances. Mental health disorders are also a serious nonmotor feature of PD[10,11]. Thus, psychotic symptoms are not uncommon among individuals with PD, with a prevalence rate of approximately 25%-30%[12,13]. In this regard, the study of mechanisms, as well as the search for ways to prevent and treat PD, is not only an important medical problem but also a social problem[14].

A growing body of evidence has demonstrated that glutamatergic neurotransmission plays an important role in the mechanisms of dopaminergic brain damage[15,16]. Previous studies have shown that modulation of metabotropic glutamate receptors (mGluRs) may be considered a more promising way to alter the activity of the brain glutamatergic system than direct action on ionotropic glutamate receptors of the N-methyl-D-aspartate and amino-methyl-phosphonic acid subtypes[17]. However, the neurochemical and neuropsychological effects of mGluRs on dopaminergic neurotoxicity remain poorly understood.

The association between the neurotransmitter function of glutamate and the formation of neuronal messenger nitric oxide (NO) has received increased attention in recent years. NO is considered to be the first representative of a novel family of signaling molecules with neurotransmitter properties[18,19]. NO is a labile free radical that is involved in many physiological processes[20]. It is assumed that together with some important physiological functions in the CNS, NO can have either neuroprotective or neurotoxic actions, depending on its redox state[21]. There are growing numbers of studies concerning the involvement of NO in the mechanisms of dopaminergic neurotoxicity[22-24]. Measurement of NO is technically difficult due to its rapid chemical reactions with a wide range of molecules, such as free radicals, metals, thiols, *etc*[25]. Thus, accurate detection and quantification are critical to understanding health and disease[26]. Most of the NO measurement techniques in the literature are indirect[27,28]. In our work, we used the direct electron paramagnetic resonance (EPR) method, which allows us to estimate the generation of NO radicals directly in brain tissue[29-31]. The current paper aims to review the involvement of mGluRs and the contribution of NO to dopaminergic neurotoxicity. More precisely, we focused on studies conducted on the rotenone-induced Parkinson's disease model. This review is also an outline of our own results obtained using the EPR method, which allows quantitation of NO radicals in brain structures.

MODELS OF DOPAMINERGIC NEUROTOXICITY

The use of animal models to study neurological diseases associated with dopaminergic neurotoxicity allows for in-depth study of their neuropathophysiology[32,33]. Patholo-

gically, the hallmark of idiopathic PD is the loss of dopaminergic neurons in the substantia nigra (SN). However, in the absence of nigral involvement, noncatecholaminergic neurons are also affected[34]. Agents that selectively damage or disrupt catecholaminergic systems, such as reserpine, methamphetamine (METH), 6-hydroxydopamine (6-OHDA), and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), have been used to develop PD models of PD[35,36]. Based on experimental and clinical evidence, PD was the first neurological disease to be modeled and subsequently treated with neurotransmitter replacement therapy[35]. Recent studies have shown that nigrostriatal dopamine degeneration can be induced *via* overexpression of α-synuclein using viral vectors or transgenic techniques. In addition, protein aggregation pathology can be triggered by inoculating preformed fibrils of α-synuclein in the SN or the striatum[37,38]. Transgenic animals that overexpress α-synuclein were used to study the role of this protein in dopaminergic degeneration[39,40]. Nevertheless, although transgenic models offer insight into the causes of the pathogenesis of PD or Lewy body (LB)-like formation, the lack of sequential loss of neurons in the SNc remains a major limitation for these models[40]. Conversely, toxin-based models recreate selective nigrostriatal cell death and show extensive motor dysfunction. However, these toxin models do not reproduce the extranigral degeneration that also occurs as part of the disease and lack the pathological hallmark of LB inclusions[39,41]. Betarbet *et al*[42] reported that chronic, systemic introduction of rotenone, an inhibitor of mitochondrial complex I, accurately replicates many aspects of the pathology of PD. Additionally, in rotenone-treated animals, α-synuclein-and polyubiquitin-positive aggregates were observed in dopamine neurons of the SN[43,44]. The advantages of this model include a slow and specific loss of DA neurons. The disadvantages of the model include the duration of drug administration, as well as sometimes high animal mortality[36]. Currently, several modifications of rotenone-induced Parkinson's disease models have been created. These modifications are different in the mode of administration as well as in the dosage and duration of treatment with rotenone[44-46]. The fact that rotenone is still widely used in agriculture as a pesticide increases the relevance of studying this model[47-49]. However, while the behavioral effects of rotenone administration are well characterized, the mechanisms of rotenone action are still poorly understood.

MGLURS IN MODELS OF DOPAMINERGIC NEUROTOXICITY

A significant number of studies have revealed that the excitotoxicity of glutamate contributes to the development of dopaminergic neurotoxicity[50-52]. It has been reported that various neurotoxic agents, including rotenone and METH, can severely damage both ionotropic and metabotropic glutamate receptors, which leads to the progression of toxic effects[53]. An important functional interplay between the dopaminergic and glutamatergic systems has stimulated the consideration of mGluRs as potential therapeutic targets in PD[54-56]. Eight mGluRs (GRM1 to GRM8) have been identified and divided into three groups based on their sequence similarity and pharmacology[57,58]. All mGluRs are family C G-protein-coupled receptors that participate in the modulation of synaptic transmission and neuronal excitability throughout the CNS[59]. Studies have shown that mGluR-mediated mechanisms have been implicated in both neuroprotection and neurotoxicity. The involvement of mGluRs in the control of movement, spatial and olfactory memory and nociception has been demonstrated[57,60,61]. Studies have shown the antiparkinsonian potential of mGluR modulation in groups I, II and III in experimental MPTP and 6-OHDA models of PD[56,62]. It has been reported that group I mGluR antagonism and groups II and III mGluR activation improve some motor symptoms of PD by regulating excitatory and inhibitory transmission in the basal ganglia[55]. However, the mechanism by which these mGluR ligands may alleviate the symptoms of parkinsonism in animal models is largely unknown.

Involvement of mGluRs in neurotoxicity induced by rotenone

Because the rotenone model of PD has attracted much attention, we searched the PubMed and Google Scholar databases for articles concerning the effect of mGluR on the rotenone model of neurotoxicity. In the end, by consensus, primary articles were selected as relevant to our goals (Table 1). Thus, it has been reported that the application of a group III mGluR agonist (L-AP-4) significantly reduced the toxicity of rotenone in a culture of TH+ midbrain neurons[63]. The authors hypothesized that activation of group III mGluR decreases the selective toxicity of rotenone to dopamine

Table 1 Main findings on metabotropic glutamate receptors involvement in rotenone-induced neurotoxicity

Ref.	Object of study	mGluR type	Ligand
Luo *et al*[67], 2019	Cell culture; rats	mGluR5	Antagonist MPEP
Bai *et al*[66], 2018	Cell culture	mGluR5	Agonist CHPG; antagonist MPEP
Xia *et al*[65], 2015	Cell culture, rats	mGluR5	Antagonist MPEP
Bashkatova *et al*[69], 2012	Rats	mGluR5	Antagonist MPEP
Sun *et al*[64], 2012	Cell culture, rats	Group I mGluR	Agonist DHPG
Zhu *et al*[68], 2012	Cell culture, rats	mGluR5	Antagonist MPEP
Alam *et al*[70], 2009	Rats	mGluR5	Antagonist MPEP
Jiang *et al*[63], 2006	Cell culture	Group III mGluR	Agonist L-AP-4

mGluR: Metabotropic glutamate receptors; MPEP: 2-methyl-6-(phenylethynyl) pyridine; CHPG: (RS)-2-chloro-5-hydroxyphenylglycine; DHPG: (S)-3,5-dihydroxyphenylglycine.

neurons by activating the MAP kinase pathway to stabilize microtubules[63]. In contrast, activation of group I mGluRs enhances rotenone-induced toxicity in MN9D cells[64]. The modulation of the mGluR5 type in rotenone-induced PD models has attracted much attention from researchers. Pharmacological inhibition of mGluR5 has beneficial anti-akinetic effects in animal models of PD; however, the mechanism by which these antagonists alleviate PD symptoms is largely unknown[65]. Previous studies have shown that downregulation of mGluR5 promotes cell apoptosis in a model of rotenone-induced cellular PD. Moreover, conditioned media derived from rotenone-treated dopaminergic MN9D neuronal cells have been found to enhance the production of reactive oxygen species (ROS), which can be further attenuated by an mGlu5 agonist[66]. The selective mGluR5 antagonist 2-methyl-6-(phenylethynyl) pyridine (MPEP) prevented rotenone-induced DNA damage in MN9D dopaminergic neurons through a mechanism involving ROS-related mitochondrial dysfunction[65]. It has been demonstrated that mGluR5 expression is decreased in a time- and dose-dependent manner in rotenone-treated MN9D cells[67]. It has been reported that oxidized extracellular cysteine/cystine redox potential plays a role in mGluR5 activity in the rotenone rat model of PD[68]. In our studies, MPEP (3 mg/kg) reduced the intensity of catalepsy in rats after long-lasting administration of rotenone at a dose of 1.5 mg/kg[69]. We observed that the mGluR5 antagonist partially prevented the increase in NO generation evoked by rotenone[69]. In another study, it was shown that the behavioral effects of MPEP (2.5 mg/kg) were less pronounced in rats receiving a higher dose of rotenone (2.5 mg/kg) following the same duration of neurotoxin administration[70]. It has been reported that coadministration of MPEP with rotenone reduces the descent latency in the grid test at day 60 but does not block the decrease in DA and serotonin levels induced by treatment with this neurotoxin[70]. Thus, the behavioral effects of mGluR5 were notably dependent on the dose of rotenone administered. The above findings indicate that mGluR5 inhibition produces an inhibitory effect on ROS and NO activity[65,66,69]. In summary, an analysis of the literature data supports the notion that antagonists of mGluR5 are considered promising targets for the treatment of pathological conditions induced by dopaminergic neurotoxicity.

INVOLVEMENT OF NO IN DOPAMINERGIC NEUROTOXICITY

NO as neuronal messenger

Currently, mitochondrial dysfunction is thought to be associated with NO pathways in glutamate neurotoxicity[71]. NO is a gaseous chemical messenger that modulates many functions of the nervous system, including the release of neurotransmitters, interneuronal communication, synaptic plasticity, receptor state, and intracellular signal transduction[20,72]. The role of NO as a biological mediator is primarily determined by its physical and chemical properties. NO is generated by the enzyme NO synthase (NOS), which is widely distributed in the brain[19,73]. One of the possible mechanisms of the neurotoxic effect of NO may be the reaction of NO with

ROS, leading to the formation of a highly toxic product peroxynitrite[24,74,75]. The short half-life of the NO radical is 2-5 s[20]. There are several indirect methods for determining NO and its products/metabolites in biological fluids and tissues. One of the most frequently used indirect methods for the determination of NO is the measurement of nitrite and nitrate by spectroscopy using the Griess reagent[27]. Another well-known method for indirect measurement of NO is the quantitative determination of 3-nitrotyrosine (a product of tyrosine nitration)[76]. The applicability of these indirect methods seems to be problematic. Quantitative determination of nitrites by the Griess method is falsified in the presence of reducing agents as well as thiol groups[77]. These data are consistent with our opinion that only direct methods may be used for reliable determination of NO levels. One of the most accurate and correct ways to measure these data is through use of the EPR method[26,31,78,79].

Participation of no in dopaminergic neurotoxicity

Recent reports claim that NO is involved in neurotoxicity elicited by dopaminergic neurotoxins[24,74,79]. Over the past two decades, significant advances have been made in improving knowledge about the role of NO in the mechanisms of PD pathogenesis[21,80,81]. Thus, in brains from victims of PD, a nitrosyl species, identified as nitrosyl hemoglobin, has been observed in the SN[82]. Previous studies have shown that neurotoxic agents such as MPTP[83], 6-OHDA[84] or METH[74] induce a significant increase in the production of 3-nitrotyrosine in the striatum. The protective effect of neuronal NOS inhibitors has been demonstrated in the MPTP neurotoxicity model in mice[85].

Involvement of no in neurotoxicity induced by rotenone

NO is cytotoxic, partly due to its effects on mitochondria[86]. Research reports have shown that NO is involved in rotenone-induced neurotoxicity (Table 2). However, the detailed mechanisms of this process are not well understood. Our data indicate that following a single injection of rotenone (1.5 mg/kg), the levels of NO in all studied brain areas were indistinguishable from those in control animals[78]. The data obtained correspond with the results of other authors. Thus, acute administration of rotenone at a significantly higher dose (15 mg/kg) did not affect the level of hydroxyl radical generation[87]. The NO level reached its maximum in dopaminergic structures, the prefrontal cortex, and the NAc 60 d after administration of rotenone[78]. We observed a more than 2-fold elevation in NO generation in all studied brain structures of rats only after repeated injections of rotenone[78]. These results are consistent with other studies investigating NO metabolites/products in the brains of rats treated with rotenone (Table 2). Thus, a significant increase (by 200.0%) in the concentration of nitrite determined by the spectrophotometric method was observed[88]. Authors suggest that overproduction of NO may be associated with Snitrosylation or nitration of certain important proteins[88]. It was reported that the production of 3-nitrotyrosine in the brains of rats treated with rotenone for 40 d increased significantly[76]. In recent years, several studies have investigated the potential neuroprotective properties of various plant extracts[89-91], polyphenolic agents[92] and flavonoids[93] in a rotenone model of PD. The authors measured the level of nitrites as a marker of neurotoxicity in the dopaminergic brain structures of animals after long-lasting administration of rotenone (Table 2). The above studies indicate that the content of NO and its metabolites in the brain is currently considered one of the markers of rotenone-induced neurotoxicity.

In our opinion, it seems to be critical to study the dynamics of NO changes in various brain structures during long-term administration of rotenone. This issue is practically not studied. Our results demonstrated a significant enhancement of NO generation in the NAc after 20 d of treatment with rotenone, while the NO level was not elevated yet in the frontal cortex[78]. These data may indicate that dopaminergic neurons in the NAc may be intrinsically susceptible to oxidative damage compared to other neurons. Taken together, our results, as well as literature data, allow us to conclude that rotenone can produce a neurotoxic effect and cause an increased production of free radicals, including NO, only with long-lasting chronic administration. This, in turn, confirms the assumption that the cascade of biochemical reactions causing the development of neurotoxic processes can be triggered only after repeated injections of rotenone[35,78,87,94]. In summary, the data obtained indicate prospects for further research on the interaction of dopaminergic, mGluR and NO systems in rotenone models of PD to search for and study the mechanism of action of substances with neuroprotective properties (Figure 1).

Table 2 Main finding on the determination of nitric oxide and its products/metabolites in the rotenone model of neurotoxicity

Ref.	Dose of rotenone	Duration	NO or its products/metabolites	Method of NO determination
Kumar *et al*[91], 2021	2.0 mg/kg	28	Nitrite	Spectrophotometry
Parkhe *et al*[92], 2020	2.0 mg/kg	21	Nitrite	Spectrophotometry
Sharma *et al*[93], 2020	2.0 mg/kg	28	Nitrite	Spectrophotometry
Sun *et al*[80], 2019	1.5 mg/kg	28	Nitrate/nitrite	NO assay kit
Jayaraj *et al*[90], 2019	1.5 mg/kg	28	Nitrite	Spectrophotometry
Abdel-Salam *et al*[89], 2017	1.5 mg/kg × 3	7	Nitrite	Spectrophotometry
Javed *et al*[86], 2016	2.5 mg/kg	28	Nitrite	Spectrophotometry
Xiong *et al*[88], 2015	1.5 mg/kg	6	Nitrite	Spectrophotometry
Tapias *et al*[23], 2014	3.0 mg/kg	Individually[1]	3-NT (3-nitrotyrosine)	Immunofluorescence
Bashkatova *et al*[69], 2012	1.5 mg/kg	60	NO (Nitroxyl radical)	EPR
Bashkatova *et al*[78], 2004	1.5 mg/kg	60	NO (Nitroxyl radical)	EPR
He *et al*[76], 2003	2 mg/kg × 3	40	3-NT (3-nitrotyrosine)	HPLC

[1]Tissue collection was carried out when each individual animal had reached endpoint (when the behavioral phenotype became debilitating, *i.e.*, when akynesia, rigidity, and postural instability were manifested)[23]. NO: Nitric oxide; EPR: Electron paramagnetic resonance; HPLC: High performance liquid chromatography.

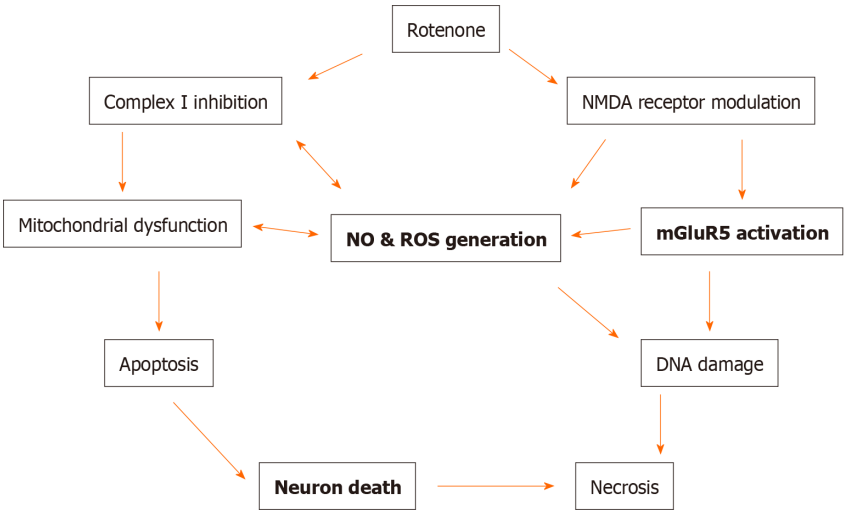


Figure 1 Proposed scheme for the involvement of nitric oxide and metabotropic glutamate receptor subtype 5 in rotenone-induced dopaminergic neurotoxicity. It is now generally accepted that rotenone in low doses of rotenone specifically binds complex I and induces mitochondrial dysfunction. The action of rotenone can be mediated by an increase in the N-methyl-D-aspartate current, which leads to the activation of metabotropic glutamate receptor subtype 5. Complex I, in combination with excitation of glutamate receptors, induces the generation of reactive oxygen species and nitric oxide. In summary, these key cellular events induce progressive death of dopaminergic neurons in the substantia nigra pars compacta *via* apoptosis and necrosis. It is important to note that at each stage, the action of rotenone becomes regionally limited so that inhibition of complex I ultimately lead to highly selective degeneration and loss of dopaminergic neurons of the nigrostriatal pathway. NO: Nitric oxide; ROS: Reactive oxygen species.

CONCLUSION

This review summarizes several newly discovered mechanisms of dopaminergic neurotoxicity (Figure 1). Current treatments for PD are mainly the administration of dopaminergic drugs. However, dopaminergic drugs are only symptomatic treatments and are limited by several side effects. Understanding the pathogenetic mechanisms of the onset and development of PD is of great clinical importance. Recent studies on drug development have focused on emerging new molecular mechanisms, including modulation of mGluRs and NO formation. Despite the growing number of studies demonstrating the positive effect of some mGluR ligands on motor symptomatology in PD models, there are still no drugs in clinical practice targeting mGluRs to restore

neurological disorders of PD. Treatment with NO scavengers/NOS inhibitors may be another potential neuroprotective strategy for diseases associated with dopaminergic neurotoxicity. In addition, our preliminary results and literature data suggest that an increase in the formation of NO radicals in some brain structures may precede the onset of behavioral disorders in rats treated with rotenone. Therefore, finding a possible correlation between the generation of NO radicals and the onset of neurological disturbances during long-term application of rotenone can be an important step in understanding the pathogenesis of rotenone-induced neurotoxicity We can assume that in the future, the determination of NO generation may become a test for the early diagnosis of PD in patients who do not yet have specific symptoms of the disease.

Additionally, long-term application and widespread use of synthetic insecticides have resulted in the accumulation of their residues in food, milk, water, and soil and have adverse health effects for humans[95]. Although all natural insecticides are not completely safe, it seems necessary to phase out the use of rotenone pesticides in agriculture and replace them with natural ("organic") pesticides with maximum safety.

In summary, alternative treatment strategies beyond dopaminergic drugs might be a major topic of future PD therapy. In conclusion, the findings demonstrate that modulation of mGluR and NO formation suggests the possibility of developing new treatment strategies for PD.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 841-853

DOI: 10.5498/wjp.v11.i10.841

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Factors causing a relapse of major depressive disorders following successful electroconvulsive therapy: A retrospective cohort study

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Author contributions: Kurimoto N contributed to the conception of the study, acquisition of the data, analysis and interpretation of the data, and drafting of the manuscript; Kuriyama K contributed to the interpretation of the data, drafting the manuscript, critical review, and support of the entire study project; Kadotani H and Yamada N contributed to the analysis and interpretation of the data and critical review; Inagaki T and Aoki T contributed to the acquisition of the data and critical reviews; Kurimoto F and Ozeki Y contributed to the critical review; all authors wrote, read and approved the final manuscript.

Supported by MHLW Practical Research Project for Life-Style related Diseases including Cardiovascular Diseases and Diabetes program, No. 21FA0201; and MEXT/JSPS, No. 17H00872.

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Abstract

BACKGROUND

Electroconvulsive therapy (ECT) is used to treat major depressive disorder (MDD). Relapse is often observed even after successful ECT, followed by adequate pharmaceutical treatment for MDD.

AIM

To investigate the diagnostic factors and treatment strategies associated with depression relapse.

METHODS

We analyzed the relationships between relapse, the diagnostic change from MDD to bipolar disorder (BP), and treatment after the initial ECT. We performed a 3-year retrospective study of the prognoses of 85 patients of the Shiga University of Medical Science Hospital. The relative risk of relapse of depressive symptoms was

Institutional review board statement: The study protocol was approved by the Shiga University of Medical Science Ethics Committee (27-178) and registered in the UMIN-CTR (UMIN000030458).

Informed consent statement: All patients provided informed consent through an opt-out methodology.

Conflict-of-interest statement: NK reports honoraria for lectures from Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Janssen Pharmaceutical K.K. TI reports honoraria for lectures from Otsuka Pharmaceutical Co., Ltd., Yoshitomiyakuhin Corporation, Lundbeck Japan K.K., and Janssen Pharmaceutical K.K.; honoraria for manuscript writing from Kitaohji Syobo, Maruzen Publishing Co., Ltd., and SEIKAISHA Ltd. KK reports grants from Otsuka Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., MSD K.K., Eisai Co., Ltd., Takeda Pharmaceutical Co., Ltd., Pfizer Jaoan Inc., Shionogi Pharma Co., Ltd., Mitsubishi-Tanabe Pharma Corporation, Tsumura and Co., and Kao Corporation, and honoraria for lectures from Meiji Seika Pharma Co., Ltd., Eli Lilly Japan K.K., Eisai Co., Ltd., MSD K.K., Yoshitomiyakuhin Corporation, Tsumura and Co., and Takeda Pharmaceutical Co., Ltd. H.K. is associated with a laboratory that is supported by donations from Fukuda Lifetech Co., Ltd., Fukuda Life Tech Keiji Co., Ltd., Tanaka Sleep Clinic, Akita Sleep Clinic, and AiAi Care Co., Ltd., Shiga University of Medical Science. H.K. received grants from Eisai Co., Ltd., and Merck Sharp and Dohme Corp/MSD K.K. (Investigator-Initiated Studies Program). HK reports honoraria for lectures from Eisai Co., Ltd., Nobelpharma Co., Ltd. Shiga prefecture, honoraria for manuscript writing from Nipponrinsyosya Co., Ltd., Life Science, and Asakura Publishing Co., Ltd., and consulting fees from Takeda Pharmaceutical Co., Ltd.

calculated based on the diagnostic change from MDD to BP. A receiver operating characteristic (ROC) curve was generated to evaluate the predictive accuracy of diagnostic changes from MDD to BP based on the duration between the first course of ECT and the relapse of depressive symptoms.

RESULTS

Eighty-five patients initially diagnosed with MDD and successfully treated with ECT were enrolled in the study. Compared with the MDD participants, more BP patients experienced relapses and required continuation and/or maintenance ECT to maintain remission (65.6% *vs* 15.1%, $P < 0.001$; relative risk = 4.35, 95%CI: 2.19-8.63, $P < 0.001$). Twenty-nine patients experienced relapses during the three-year follow-up. In 21 (72.4%, 21/29) patients with relapse, the diagnosis was changed from MDD to BP. The duration from the first course of ECT to relapse was shorter for the BP patients than for the MDD patients (9.63 ± 10.4 mo *vs* 3.38 ± 3.77 mo, $P = 0.022$); for most patients, the interval was less than one month. The relative risk of depressive symptoms based on diagnostic changes was 4.35 (95% confidence interval: 2.19–8.63, $P < 0.001$), and the area under the ROC curve for detecting diagnostic changes based on relapse duration was 0.756 (95%CI: 0.562-0.895, $P = 0.007$).

CONCLUSION

It may be beneficial to suspect BP and change the treatment strategy from MDD to BP for patients experiencing an early relapse.

Key Words: Electroconvulsive therapy; Major depressive disorder; Bipolar disorder; Antidepressant; Prognosis; Relapse

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Core Tip: Patients who are diagnosed with major depressive disorder (MDD) but repeatedly relapse after electroconvulsive therapy (ECT) and require continuation and/or maintenance electroconvulsive therapy (C/M-ECT) may be in the depressive phase of bipolar disorder (BP). Rather than repeating C/M-ECT alone, even without obvious manic symptoms, the treatment for MDD may have to be revised to that for BP for patients who relapse within one month.

Citation: Kurimoto N, Inagaki T, Aoki T, Kadotani H, Kurimoto F, Kuriyama K, Yamada N, Ozeki Y. Factors causing a relapse of major depressive disorders following successful electroconvulsive therapy: A retrospective cohort study. *World J Psychiatr* 2021; 11(10): 841-853

URL: https://www.wjgnet.com/2220-3206/full/v11/i10/841.htm

DOI: https://dx.doi.org/10.5498/wjp.v11.i10.841

INTRODUCTION

Treatment options for major depressive disorder (MDD) resistant to pharmaceutical therapy are extremely limited[1]. Currently, electroconvulsive therapy (ECT) is the most promising therapeutic modality for MDD, including drug-resistant depression[2,3]. The efficacy of ECT is reportedly 50%–60% for drug-resistant depression, irrespective of the presence of psychotic features[4]. However, most ECT-treated patients who continue pharmacotherapy experience relapse within 6 mo after receiving adequate ECT[5,6].

Thus, some maintenance therapies after adequate ECT are usually utilized to prevent relapse if the initial therapy results in the complete remission of depression. It has been reported that maintenance therapy with a combination of lithium and an antidepressant is more effective than antidepressants alone[7,8]. Moreover, cumulative evidence suggests that continuation and/or maintenance ECT (C/M-ECT) combined with pharmacotherapy maintains a significantly higher remission rate several months after the initial ECT[9,10]. Recent reviews and meta-analyses have recommended

Grants and personal fees from companies are not directly related to this study. The opinions expressed in this paper are those of the authors and do not necessarily represent those of companies including Merck Sharp and Dohme Corp/MSD K.K. The other authors declare no conflicts of interest.

Data sharing statement: The datasets analyzed in the current study are available from the corresponding author upon reasonable request at kadotanisleep@gmail.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Japan

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 28, 2021
Peer-review started: March 28, 2021
First decision: July 15, 2021
Revised: July 26, 2021
Accepted: August 30, 2021

C/M-ECT combined with pharmacotherapy for MDD[11,12].

However, it remains unclear whether the recommended therapeutic strategy obscures the potential risk of a future manic episode since both ECT and mood stabilizers, such as lithium, are effective for both depressive and manic symptoms. A considerable proportion of patients with bipolar disorder (BP) are misdiagnosed with MDD at their first visit[13-15] because their episodes emerge as depression more often than mania.

Several studies have reported a diagnostic change from MDD to BP during the treatment of MDD[14-18]. However, the prognosis of antidepressant-resistant depressive patients after remission using ECT has not been systematically investigated. Therefore, we hypothesized that remission of depression after ECT followed by a relapse, even after receiving an antidepressant-based maintenance therapy without any mood stabilizers, is indicative of BP. To test our hypothesis, we conducted a retrospective cohort study involving a 3-year follow-up of patients who experienced remission of depression after undergoing ECT at our hospital.

MATERIALS AND METHODS

Participants

We recruited patients who were admitted to the Department of Psychiatry at the Shiga University of Medical Science Hospital and had their first ECT between January 2009 and December 2011.

Diagnoses of inpatients in the psychiatry department, based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[19], were routinely made by the consensus of multiple psychiatrists who are members of the Japanese Board of Psychiatry at weekly conferences. Decisions to change the diagnosis of manic/hypomanic episodes from MDD to BP were also made during the conferences. We included patients who were initially diagnosed with MDD (n = 112) without any other mental or neurological disorders (Figure 1). Patients who were initially diagnosed as BP or with BP mixed episodes were not included in this study.

Definitions of remission and relapse

We defined successful remission after ECT as follows: (1) The patient no longer conformed to the diagnostic criteria for MDD; (2) the Hamilton Depression Scale 21-Item (HAMD-21)[20] score improved by ≥ 60% since admission; and (3) the patient was discharged and resumed normal activity at home.

Relapse was defined as the reappearance of five or more symptoms of the diagnostic criteria for MDD.

Criterion for changing diagnosis

When there was a manic/hypomanic episode meeting the DSM-IV-Text Revision (DSM-IV-TR)[19] criteria during the follow-up, the diagnosis was changed to BP. BP I and II were diagnosed when the patients had manic and hypomanic episodes, respectively. Diagnostic changes and changes in treatment strategy from MDD to BP among inpatients were made within one week after the first manic/hypomanic episodes were observed. Manic/hypomanic episodes of outpatients were determined when manic/hypomanic symptoms persisted for at least more than a couple of days. Moreover, when other psychotic and epileptic symptoms were dominant and met the DSM-IV-TR[19] diagnostic criteria, the diagnosis was changed to schizophrenia and epilepsy, respectively.

The patients were typically treated with antidepressants according to the American Psychiatric Association (APA) guidelines[4]. ECT was carefully applied according to the APA Practice Guideline[4] and the National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom[21]. At least one of the following criteria was met for the administration of ECT to patients with MDD: (1) The patients did not experience remission despite receiving a sufficient dose of two or more antidepressants (drug resistance); (2) The patients had serious suicidal thoughts; and (3) It was difficult to administer pharmacotherapy, such as when patients were unable to take food and oral medications due to psychomotor retardation or hypobulia.

We excluded patients who failed to achieve remission after the first ECT (n = 11) and those who were diagnosed with schizophrenia (n = 3), epilepsy (n = 1), chronic pain (n = 2), or Alzheimer's disease (n = 4) during the follow-up. We could not follow up 6 patients for the duration after the first ECT, as they moved out (Figure 1).

Article in press: August 30, 2021
Published online: October 19, 2021

P-Reviewer: Chakrabarti S
S-Editor: Wang LL
L-Editor: A
P-Editor: Guo X

Eighty-five participants, with a significant improvement in depressive symptoms and remission after the first successful course of ECT, were naturally observed. Depression severity and psychosocial dysfunction were assessed using the HAMD-21 [20] and the Global Assessment of Functioning scale (GAF) of the DSM-IV-TR[19]. The duration of the follow-up observation was set to 36 mo after remission was achieved with the first course of ECT. Anxiety symptoms were not included in this study, which were not included in the diagnostic criteria for MDD in the DSM-IV-TR.

The study was conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was not obtained because of the retrospective nature of the study. We displayed the study protocol on the hospital's website and outpatient units of the hospital. The participants were offered the opportunity to opt out of the study. The study protocol was approved by the Shiga University of Medical Science Ethics Committee (27-178) and registered in the UMIN-CTR (UMIN000030458).

We obtained patient data from the medical records: Age, sex, number, and date of ECT, HAMD-21, GAF, diagnosis, onset of disease, medication, psychotic features, and depressive symptoms. These were all essential medical data for ECT and were cross-checked with the doctors in charge. No missing data were included in the study.

Group classification

The participants were retrospectively classified into four groups based on their clinical course (Figure 1). Four groups were included and analyzed in this study.

Groups A and B

Fifty-six participants who did not experience a relapse of depressive symptoms after the first course of ECT were classified as A and B. The patients were treated with pharmacotherapy based on their respective diagnoses.

Group A included 45 participants with MDD; 40 remained in remission with treatment with a continuous single antidepressant, and five remained in remission with the concomitant use of lithium and some antidepressants.

Group B included eleven participants with BP, whose diagnoses changed from MDD to BP based on the manic/hypomanic symptoms during their first course of ECT or during subsequent maintenance therapy with antidepressants. Six and five of them were diagnosed with BP I and BP II, respectively. The maintenance therapy was continued after ECT, and the antidepressant treatments were discontinued. All patients in group B were maintained in remission with mood stabilizers.

Groups C and D

Twenty-nine participants who experienced relapses of depressive symptoms after the first course of ECT were classified as C and D. All patients achieved remission after the second course of ECT and were switched to C/M-ECT with antidepressants.

Group C included eight participants with MDD: five experienced a repeated relapse of depressive symptoms and were maintained in remission with SSRIs or SNRIs; two experienced relapse and were maintained in remission on a tricyclic antidepressant and aripiprazole; and one experienced relapse but was maintained in remission on an antidepressant with lithium after C/M-ECT was discontinued.

Group D included twenty-one participants with BP whose diagnoses changed from MDD to BP because they had manic/hypomanic symptoms during C/M-ECT with antidepressants, which persisted after treatment was discontinued. Two and nineteen of them were diagnosed with BP I and BP II, respectively. Patients in this group were maintained in remission with mood stabilizers without C/M-ECT.

ECT procedures

ECT was performed using a THYMATRON SYSTEM IV ECT instrument (Somatics LLC, Lake Bluff, IL, USA). Procedures for anesthesia and the determination of seizure adequacy followed a standardized clinical protocol that was consistent with the current standards of care[3]. Anesthesia for the procedure included intravenous thiamylal (1.0 -1.5 mg/kg) and succinylcholine (1 mg/kg). The participants were pre-oxygenated and manually ventilated using a valve mask and 100% oxygen after they showed adequate muscle relaxation. The electrodes were placed bilaterally on the forehead. The electrical dose for the short-term course of ECT was estimated using the ''half age method.'' The median number of ECT sessions was 8.47 ± 3.72. The same energy required for short-term treatment was used for the second course of ECT and C/M-ECT. For the short-term course, the participants received two or three weekly sessions until remission.

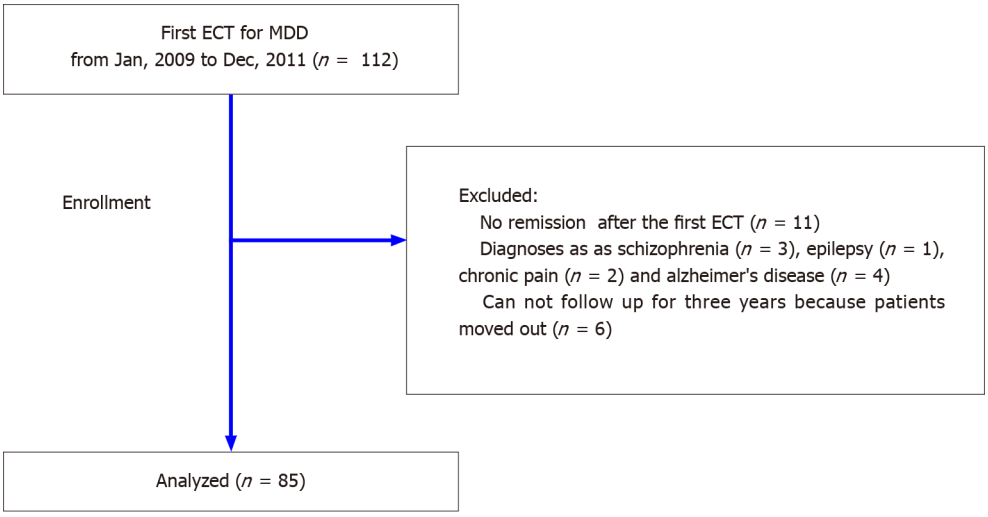


Figure 1 Flow diagram of the participants. ECT: Electroconvulsive therapy; MDD: Major depressive disorder.

Follow-up regimens

Pharmaceutical maintenance therapy was administered to all participants following the first course of ECT. Tricyclic antidepressants (TCAs) were preferentially selected for the maintenance treatment of all participants with MDD if they were tolerable. Sackeim *et al*[22] reported that nortriptyline increases remission compared to venlafaxine when concomitantly administered with ECT in patients with MDD. Venlafaxine was not available in Japan during the study period. Fifty-two participants primarily received TCAs, and 41 received selective serotonin or norepinephrine reuptake inhibitors (SSRI/SNRIs). All antidepressants were prescribed in doses equivalent to 150 mg of imipramine, which satisfied the maximum allowable dose.

When 29 of the participants experienced a relapse, a second course of ECT was administered, and remission was achieved. Subsequently, the treatment was changed to C/M-ECT with antidepressants. If no relapse was observed, the intervals for the C/M-ECTs gradually increased from one to six months.

We terminated C/M-ECT when remission was maintained for more than 6 mo or new-onset psychiatric symptoms (*e.g.*, mood-incongruent delusions) were dominant.

Statistical analyses

The clinical characteristics are presented as mean ± SD. We performed a chi-square test or *t*-test to investigate any intergroup differences in the following items as needed: (1) Demographic data (sex, age at onset, and disease duration until the first ECT session); (2) Admission data (HAMD-21 score during admission, GAF score, the presence of psychotic features, and the number of ECT performed during the first course); (3) Discharge data (HAMD-21 score during discharge, GAF score, and type of antidepressants for maintenance therapy); and (4) Post-discharge data (the period of relapse to C/M-ECT and the diagnosis 36 mo after the final ECT).

The relative risk (RR) and 95%CIs of the relapses of depressive symptoms were calculated according to the diagnostic changes from MDD to BP during the three-year follow-up. Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic accuracy of predicting diagnostic changes from MDD to BP from the duration between the first course of ECT and relapse of depressive symptoms. We used the MedCalc Software Ver. 19.7.2 (Ostend, Belgium) for statistical analyses. Statistical significance was set at $P < 0.05$. For the sensitivity analysis, we performed a non-parametric analysis (Mann-Whitney test).

Sample and power analyses were performed using G*Power 3.1.9.7 (University of Kiel, Germany). Kellner *et al*[23] reported that the average duration of relapse was 9.1 ± 7 wk after ECT. We determined to use the same sample size and SDs for the MDD and BP groups, and hypothesized that the mean difference in the relapse durations of 9 wk may be clinically significant. We used $\alpha = 0.05$, power = 0.80, mean difference = 9, and SD = 7 for the sample size estimation. In this study, we estimated the need for a sample size of 22.

The statistical methods used in this study were reviewed by Prof. Hiromu Kutsumi and Mr. Shoji Momokawa from the Center for Clinical Research and Advanced Medicine, Shiga University of Medical Science.

RESULTS

Characteristics of the participants

This study included 85 participants aged 56.0 ± 17.0 years; 31.8% of them were males (n = 27) (Table 1, Figure 1). The average initial depressive episode started at the age of 51.7 ± 17.4 years, and the first ECT was administered after 53.1 ± 83.2 mo. All participants were followed up for 36 mo. Depression was recovered by the first ECT with scores of HAMD-21 (from 22.3 ± 13.8 to 7.13 ± 5.03, P < 0.001) and GAF (from 32.9 ± 15.5 to 66.6 ± 7.70, P < 0.001).

The MDD participants included patients whose diagnosis was not changed during the three-year follow-up for the initial ECT (groups A and C in Figure 2).

The BP participants included patients whose diagnosis was changed from MDD to BP during the three-year follow-up for initial ECT (groups B and D in Figure 2).

MDD with remission participants included patients who experienced relapses of depressive episodes after the first course of ECT, who maintained remission with MDD treatment (groups C).

BP with remission participants included patients whose diagnoses were changed from MDD to BP because of manic/hypomanic symptoms during C/M-ECT with antidepressants (group D). Subjects in this group experienced relapses of depressive symptoms after the first course of ECT with antidepressants, but they maintained remission with BP treatment.

Three subjects without relapse were excluded from this study. The diagnoses of two subjects (one male and one female) were changed to schizophrenia due to psychotic episodes. The diagnosis of another man was changed to epileptic psychosis because of his past convulsive seizure episodes with psychotic features.

Seven subjects with relapse were also excluded from the study. Four subjects (two women and two men) had their diagnoses changed to concomitant MDD and Alzheimer's dementia due to their consistent mnemonic impairments; two males had their diagnoses changed to concomitant MDD and chronic pain, and another male had his diagnosis changed to schizophrenia.

Diagnostic group-specific characteristics (MDD vs BP)

We compared the demographic data of the participants whose MDD diagnosis did not change during the three-year follow-up (Groups A and C) and those whose diagnosis was changed to BP (Groups B and D). There were no significant differences between the two groups related to sex, age, age of onset, and HAMD-21/GAF scores during admission or discharge (Table 1). However, the duration from the onset of depression to the first ECT was significantly shorter in the MDD participants (Groups A and C) than in the BP participants (Groups B and D) (33.5 ± 48.1 *vs* 85.8 ± 114.9%, P = 0.009), while psychotic features were more prominent in the MDD participants (43.4% *vs* 21.9%, P = 0.046).

The MDD and BP participants with remission (Group C *vs* D) had similar demographic data, except for the duration from the first course of ECT to relapse (Table 1).

Diagnostic change due to manic/hypomanic episodes

Of the 85 participants, 32 (37.6%) had their diagnosis changed to BP because of manic/hypomanic episodes experienced after remission after the first ECT or during the C/M-ECT period (Groups B and D; Figure 2).

Higher risk of relapse among patients with diagnostic changes than those without

We observed a significantly higher risk of relapse in the diagnostic change groups (Groups B and D) than in the unchanged groups (Groups A and C) (RR = 4.35, 95%CI: 2.19-8.63, P <0.001). A higher percentage of relapses was found in participants whose diagnosis was changed from MDD to BP (65.6%: Group D/Groups B + D) than in those whose diagnosis was MDD (15.1%: Group C/Groups A + C) (P <0.001) (Figure 2). In addition, the types of antidepressants (SSRI/SNRI or TCA) for maintenance therapy were similar among the groups (Groups A, B, C, and D) (chi-square test, P = 0.77).

Period until relapse

We investigated the duration from the first course of ECT to the relapse of depressive symptoms in the patients with MDD and BP (groups C and D). The relapse was significantly earlier in the group with a change in the diagnosis to BP (Group D) than in the group without any diagnostic changes (Group C). (t-test, P = 0.022; Figure 3). As

Table 1 Characteristics of the participants

Variables	Total	MDD patients	BP patients	*P* values	MDD with remission	BP with remission	*P* values
n	85	53	32		8	21	
Male, n (%)	27 (31.8)	16 (30.2)	11 (34.4)	0.690	2 (25.0)	7 (33.3)	0.670
Age, yr	56.0 ± 17.0	56.6 ± 17.6	55.0 ± 16.1	0.676	55.0 ± 21.3	51.9 ± 14.9	0.656
Onset age, yr	51.7 ± 17.4	53.7 ± 18.3	48.5 ± 15.3	0.179	51.4 ± 23.3	47.0 ± 13.2	0.527
Duration from onset to first ECT, mo	53.1 ± 83.2	33.5 ± 48.1	85.8 ± 115	0.009	36.9 ± 37.9	67.1 ± 86.1	0.385
Psychotic features, *n* (%)	30 (35.3)	23 (43.4)	7 (21.9)	0.046	3 (37.5)	5 (23.8)	0.469
HAMD-21 on admission	22.3 ± 13.8	24.4 ± 15.1	18.9 ± 10.9	0.079	26.4 ± 11.0	19.1 ± 10.2	0.103
HAMD-21 on discharge	7.13 ± 5.03	6.77 ± 4.14	7.72 ± 6.26	0.008	8.75 ± 4.59	6.90 ± 5.43	0.403
GAF on admission	32.9 ± 15.5	31.0 ± 16.0	36.0 ± 14.5	0.150	37.9 ± 9.88	39.0 ± 16.0	0.861
GAF on discharge	66.6 ± 7.70	66.4 ± 7.52	67.0 ± 8.08	0.720	66.5 ± 9.07	69.2 ± 5.97	0.348
Duration from first ECT to relapse, mo					9.63 ± 10.4	3.38 ± 3.77	0.022

Results showed as mean ± SD. MDD: Major depressive disorder; BP: Bipolar disorder; ECT: Electroconvulsive therapy; HAMD-21: Hamilton Depression Scale; GAF: Global Assessment of Functioning Scale.

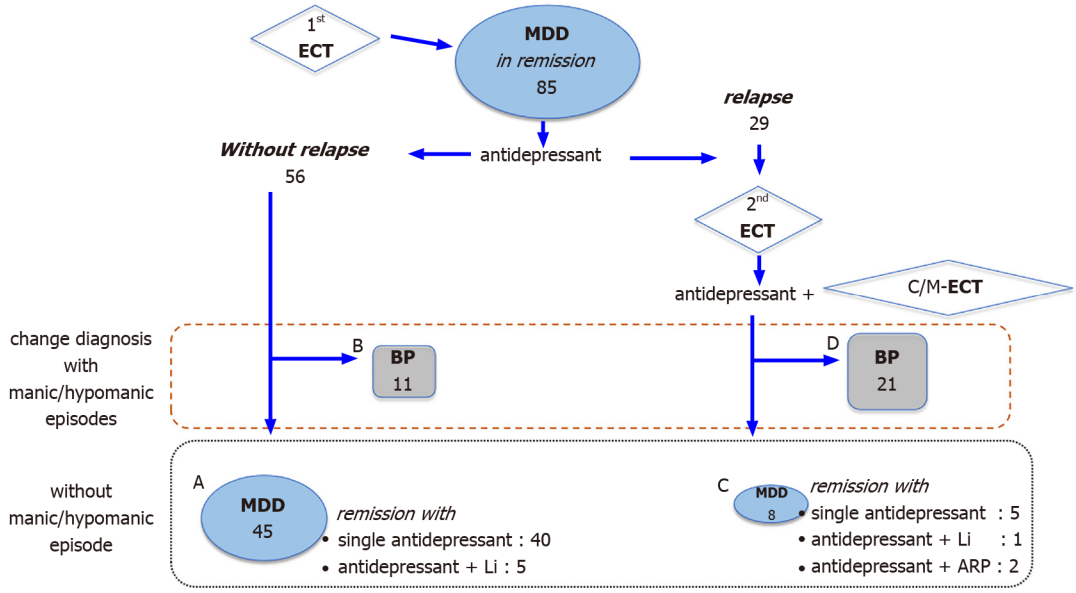


Figure 2 Changes in the treatment and diagnosis based on the relapse and manic/hypomanic episodes after remission after the first electroconvulsive therapy. Relapses were characterized by five or more of the diagnostic criteria for major depressive disorder. Patients in groups A and B did not experience relapse after the first course of electroconvulsive therapy (ECT). Patients in groups C and D experienced a relapse after the first course of ECT. When there was a manic/hypomanic episode during the follow-up, the diagnosis was changed from major depressive disorder to bipolar disorder. ECT: Electroconvulsive therapy; MDD: Major depressive disorder; BP: Bipolar disorder; Li: Lithium; ARP: Aripiprazole.

a sensitivity analysis, we performed a non-parametric analysis (Mann-Whitney test) on duration from the first course of ECT to relapse between patients with MDD and BP (groups C and D), and we had a similar finding with a *P* value of 0.034.

To determine the predictive value of the duration until relapse for BP, we performed an ROC analysis (Figure 4). Of the patients who experienced a relapse of depressive symptoms within 3 mo, 75% had BP, whereas 61.9% of those who remained relapse-free for at least 3 mo had MDD.

A period of less than 1 mo to relapse demonstrated a sensitivity of 38.1% (95%CI: 18.1%-61.6%), specificity of 100% (95%CI: 63.1%-100%), and the area under the ROC curve of 0.756 (95%CI: 0.562-0.895) (P = 0.007), which indicated a moderately

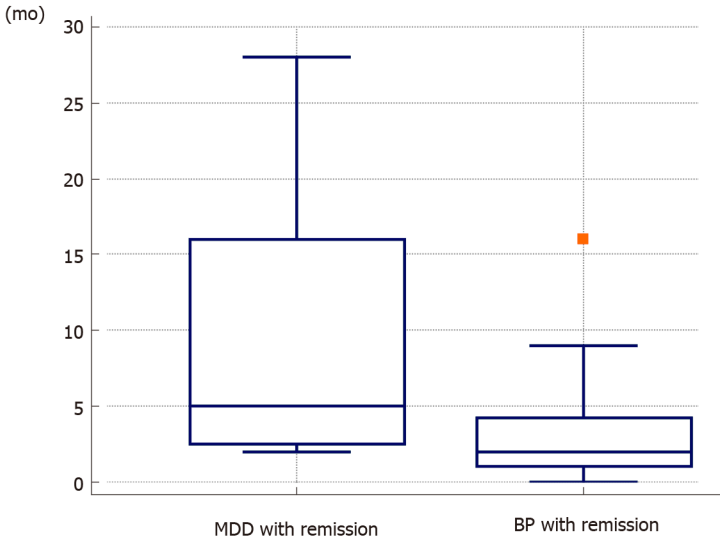


Figure 3 Period to relapse in the continuation and/or maintenance electroconvulsive therapy group. The box-and-whisker plot displays the statistical summary of the variables. The central box shows values from the lower to the upper quartiles. The middle line represents median values. The horizontal line extends from the minimum to the maximum value, excluding the outliers, which are displayed as separate points. The BP participants in group D experienced relapse significantly earlier than the major depressive disorder participants in group C.

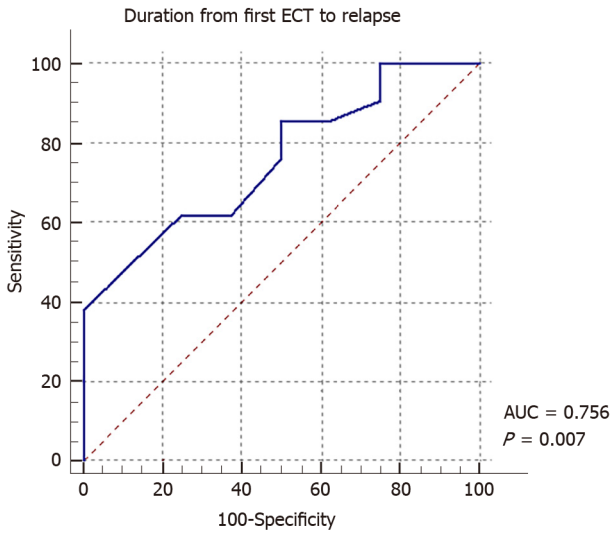


Figure 4 Receiver operating characteristic analysis for determining the accuracy of the diagnosis based on the duration of the period until relapse. Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic accuracy of predicting diagnostic changes from major depressive disorder to Bipolar disorder from the duration between the first course of electroconvulsive therapy and relapse of depressive symptoms. The area under the ROC curve to for detecting diagnostic changes by based on relapse duration was 0.756 (95%CI: 0.562-0.895, $P = 0.007$).

predictive of the diagnostic change from MDD to BP.

DISCUSSION

Patients with BP are more likely to experience relapses after ECT

We investigated the prognosis of 85 participants who were initially diagnosed with MDD, underwent ECT, and experienced remission over 3 years to identify the effect of subsequent maintenance pharmacotherapy on patients with MDD. Our results indicate that 29 participants experienced a relapse despite maintenance therapy with antidepressants after their first course of ECT and subsequently required C/M-ECT. Twenty-one participants (group D) had their diagnosis changed to BP. Therefore, BP was overlooked when potential BP patients who had depressive episodes were diagnosed with MDD, underwent ECT, and were treated with antidepressants.

Patients with BP are more likely to experience a relapse during maintenance therapy with antidepressants[24,25]. This may be a major reason for drug resistance and necessitates repeated C/M-ECT.

There are no established guidelines for the management of ECT–induced mania, and there is little evidence to guide clinicians beyond case reports and clinical experience[26]. A case report by Lee *et al*[27] described ECT-induced mania treated by aborting ECT and adding a mood stabilizer. Another case report by Thomas *et al*[26] described ECT-induced mania treated with repeated ECT alone. In this study, we aborted ECT and used mood stabilizers to treat ECT–induced mania.

Generally, a large proportion of patients with BP-associated depression may be misdiagnosed with MDD and initially treated with antidepressants alone. Regardless of treatment resistance, their diagnoses changed from MDD to BP during treatment [14-18]. In agreement with this, we found that the proportion of participants whose diagnosis was changed from MDD to BP during the maintenance treatment was similar to or higher than those reported in previous studies, although those studies involved smaller samples or reported shorter follow-ups than the current study[14-18]. To our knowledge, this is the first report to date that focuses on the possibility that patients with MDD, for which ECT is repeatedly indicated, may experience the depressive phase of BP. When patients have never experienced manic/hypomanic episodes, they cannot be diagnosed with BP; therefore, they remain diagnosed with MDD and are treated with maintenance antidepressant therapy until a first manic/hypomanic episode occurs.

Predictors of conversion to BP include the prevalence of psychotic depression[28]. Psychotic features were not prevalent among patients diagnosed with BP in this study, which may be related to the relatively old age of the patient group in this study (51.7 ± 17.4 years).

Requirements of augmentation pharmacotherapy as a potential predictor for future BP diagnosis

Of the 53 participants (groups A and C) who were ultimately diagnosed with MDD, 45 (84.9%) remained in remission with a single antidepressant, irrespective of the type of antidepressant (TCA or SSRI/SNRI). Although antidepressant-antipsychotic cotreatment is known to be effective in treating psychotic depression[29], there are no established guidelines for the management of MDD manifesting with psychotic symptoms after ECT.

In groups A and C, only five participants in group A and three participants in group C required lithium or aripiprazole augmentation to maintain remission (15.1%: (5 + 3)/(45 + 8)), whereas 45 participants maintained remission using a single antidepressant without requiring the use of lithium [84.9%: (40 + 5)/(45 + 8)]. Sackeim *et al*[7] (2001) indicated that the concomitant use of lithium was more effective than the use of nortriptyline alone in maintaining remission after ECT in patients with MDD. Likewise, aripiprazole has also been reported as a popular augmentation agent for the treatment of depression[30]. Although we considered the possibility that lithium augmentation could obscure the actual diagnosis, the results indicated that BP was more common in the relapse group.

A recent observational study reported no significant difference in the relapse ratio between MDD and BP after receiving ECT during a one-year follow-up[31]. However, valproate maintenance pharmacotherapy for MDD was associated with a lower risk of relapse than valproate treatment (multivariate analysis, hazard ratio: 0.091; $P = 0.022$).

In the current study, a large proportion (84.9%, 45/53) of patients with MDD remained in remission for three years with only a single antidepressant. Thus, an adequate dose of antidepressant monotherapy can maintain remission with good tolerability if the diagnosis of MDD is accurate.

These results indicate the importance of the initial diagnosis of MDD. Moreover, relapse that occurs during antidepressant maintenance therapy seems to be a major predictor of later changes in BP diagnosis.

Average time to relapse after administration of initial ECT

Relapse occurred significantly earlier in patients with BP than in those with MDD after the first course of ECT, indicating that BP depression is difficult to prevent through the pharmacological action of antidepressants. Paradoxically, a large proportion of MDD patients could maintain remission with a single antidepressant for at least 3 years if remission was achieved by ECT. A time threshold of one month until relapse may be a good predictor of BP diagnosis.

Although a large proportion of BP patients requires treatment with mood stabilizers to maintain remission, all patients who recovered from depression after ECT were treated with antidepressants. This may explain the earlier relapse in BP patients in the current study. The time-to-relapse may be a good indicator for predicting the prospective occurrence of manic/hypomanic episodes. Early and repetitive relapses of depressive symptoms may be an adequate milestone for predicting BP and for changing treatment strategies for maintaining remission[32].

Limitations

A major limitation of this study is that it was a naturalistic and retrospective cohort study based in a clinical setting. Diagnosis was based on the consensus of multiple psychiatrists, and the Structured Clinical Interview for DSM Disorders[33] was not performed in this study. Scales for BP, such as the Mood Disorder Questionnaire[34] and Bipolar Spectrum Diagnostic Scale [35], were not used. Although a family history of BP is one of the predictors of conversion to BP[28], a family history of BP was not analyzed.

Furthermore, the number of patients was relatively small from a single perspective, which could be a generalization bias. Retrospective clinical investigations could not perfectly exclude the ambiguity of diagnosis, because clinical diversity and flexibility are often required for the optimal treatment of patients. Comprehensive judgments are required for past clinical history and current agonizing symptoms for diagnosis such as mixed states, among others, for a diagnostic change. However, this study strictly adheres to a therapeutic strategy for maintaining remission using a single antidepressant. Thus, the current results ensure novelty in detecting the margin of antidepressant maintenance therapy for drug-resistant depressive patients achieving remission by ECT. With such limitations, our study suggests that C/M-ECT is commonly required for patients initially diagnosed with MDD, and the diagnosis was subsequently changed to BP. Patients diagnosed with MDD who are unable to continue using antidepressants after remission with ECT and relapse and require C/M-ECT may have BP. C/M-ECT with an antidepressant plus lithium prevents both BP and MDD relapses; however, it may have several side effects and lead to a lost opportunity for validating the diagnosis for remission.

CONCLUSION

Appropriate withdrawal from C/M-ECT and multiple dosing regimens contribute to improvements in the quality of life of patients and the suppression of medical and social welfare costs. It may be reasonable that changes from the treatment of MDD to BP can be considered for patients who experience a relapse within one month after the course of ECT, even if they do not have a manic/hypomanic episode. The development of a method to predict manic/hypomanic episodes can prevent the exacerbation of MDD and overtreatment to maintain the remission of MDD after the initial ECT.

ARTICLE HIGHLIGHTS

Research background

Certain proportions of depressed patients relapse after electroconvulsive therapy (ECT), and it is important to explore ways to maintain remission.

Research motivation

Since 2001, when Sackeim reported on the addition of lithium to antidepressants for maintenance treatment after ECT, only symptomatic measures, such as continuation of continuation and/or maintenance ECT (C/M-ECT) have been proposed, and there have been no new findings leading to a fundamental solution for more than 20 years.

Research objectives

The objective of our study was to investigate the diagnostic factors and treatment strategies associated with the relapse of depression.

Research methods

We analyzed the relationships between relapse, the diagnostic change from major depressive disorder (MDD) to bipolar disorder (BP), and treatment strategies after the initial administration of ECT. We performed a 3-year retrospective cohort study on the prognosis of 85 patients at the Shiga University of Medical Science Hospital. The relative risk of relapse of depressive symptoms was calculated based on the diagnostic changes from MDD to BP. A receiver operating characteristic (ROC) curve was generated to evaluate the accuracy of predicting diagnostic changes from MDD to BP based on the duration between the first course of ECT and the relapse of depressive symptoms.

Research results

Compared with the MDD participants, a greater proportion of BP participants experienced relapse and required continuation and/or maintenance ECT for maintaining remission. The duration from the first course of ECT to relapse was shorter for the BP than the MDD patients.

Research conclusions

Instead of repeating treatment for MDD, such as C/M-ECT with antidepressants without definitive evidence of resolution, patients who relapse after ECT and maintenance with antidepressants may benefit from changing the maintenance treatment after remission with C/M-ECT to the treatment for BP depression, which includes mood stabilizers without antidepressants.

Research perspectives

It is also necessary to develop a method for predicting the occurrence of manic episodes to prevent the exacerbation of MDD, as well as overtreatment for maintaining the remission of severe MDD after initial ECT.

ACKNOWLEDGEMENTS

We thank the staff at the Department of Psychiatry, Shiga University of Medical Science, for their assistance. We thank Prof. Kutsumi and Mr. Momokawa from the Center for Clinical Research and Advanced Medicine, Shiga University of Medical Science, for their technical and statistical support.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 854-863

DOI: 10.5498/wjp.v11.i10.854

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Determinants of mechanical restraint in an acute psychiatric care unit

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Author contributions: El-Abidi K is the principal investigator of the study, and contributed to the data collection, write all the article, take the discussion and conclusions; Mané A is the study coordination, contributed to analysis of results; Moreno-Poyato AR bibliographic reviewed for the introduction; Toll Privat A helped with the data collection; Corcoles Martinez D contributed to the analysis and interpretation of results with SPSS; Pérez-Solà V and Aceña-Domí nguez R contributed to the article review.

Institutional review board statement: The study was reviewed and approved by the Comité de Ética de la Investigación con Medicamentos del Parc de Salut Mar Institutional Review Board (Approval No.2019/8524/I).

Informed consent statement: The use of written informed consent in

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Abstract

BACKGROUND

Despite numerous attempts to reduce the use of mechanical restraint (MR), this technique continues to be widely applied in many acute psychiatric care settings. In order to reduce MR, a better understanding of the variables associated with its use and duration in different clinical environments is essential.

AIM

To determine the proportion of patients subjected to MR and the duration thereof in two acute care psychiatric units; and to identify the variables associated with the use and duration of MR.

METHODS

Descriptive study of all patients admitted to the acute psychiatric units at the Parc de Salut Mar (Barcelona, Spain) in the year 2018. The number and percentage of

this study was not necessary given the nature of the study.

Conflict-of-interest statement: No conflict of interest has been declared by the authors.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at amane@parcdesalutmar.cat.

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 22, 2021
Peer-review started: April 22, 2021
First decision: June 17, 2021
Revised: June 28, 2021
Accepted: September 3, 2021
Article in press: September 3, 2021
Published online: October 19, 2021

P-Reviewer: Sánchez-Cabrero R
S-Editor: Wang JL
L-Editor: A
P-Editor: Guo X

patients subjected to MR, as well as the duration of each episode were assessed. The following data were also registered: sociodemographic characteristics, psychiatric diagnosis, and presence of cultural and/or language barriers. Multivariate analyses were performed to assess determinants of MR and its duration.

RESULTS

Of the 464 patients, 119 (25.6%) required MR, with a median of 16.4 h per MR. Two factors - a diagnosis of psychotic disorder [Odds ratios (OR) = 0.22; 95%CI: 0.06-0.62; *P* = 0.005] and the presence of a language barrier (OR = 2.13; 95%CI: 1.2-3.7; *P* = 0.007) - were associated with a significantly higher risk of MR. Male sex was associated with a longer duration of MR (B = -19.03; 95%CI: -38.06-0.008; *P* = 0.05).

CONCLUSION

The presence of a language barrier and a psychotic disorder diagnosis are associated with a significantly higher risk of MR. Furthermore, male sex is associated with a longer duration of MR. Individualized restraint protocols that include the required tools are necessary to ultimately limit the use of mechanical restraint.

Key Words: Mechanical restraint; Prolonged restraint; Determining factors; Psychiatric acute unit

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Core Tip: The purpose of this descriptive study was to determine the proportion of patients subjected to mechanical restraint (MR) and the duration thereof in two acute care psychiatric units. Secondly, to identify the variables associated with the use and duration of MR. The most important highlights show that the MR remains frequent and with a median duration of more than 16 h. The diagnosis of psychotic disorder and the presence of a language barrier were associated with a significantly higher risk of MR. Furthermore, male sex was associated with a longer duration of MR.

Citation: El-Abidi K, Moreno-Poyato AR, Toll Privat A, Corcoles Martinez D, Aceña-Domínguez R, Pérez-Solà V, Mané A. Determinants of mechanical restraint in an acute psychiatric care unit. *World J Psychiatr* 2021; 11(10): 854-863
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/854.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.854

INTRODUCTION

Mechanical restraint (MR) is defined as the immobilization of a person through the application of mechanical devices that cannot be easily controlled or removed to prevent free movement of their body[1] . The use of MR in hospitalized psychiatric patients remains controversial, in part due to the numerous ethical, legal and clinical questions associated with this practice[2].

In clinical practice, MR is considered an emergency procedure for patients exhibiting potentially dangerous behaviour associated with psychiatric illnesses who have failed to respond to less restrictive interventions (principle of proportionality)[2,3]. In addition to protecting the patient from himself, MR also serves to ensure the safety of healthcare personnel and others, and/or to prevent damage to buildings and physical objects[4]. The application of MR must be carefully considered given that it deprives the individual of their freedom[5] and is also often accompanied by mandatory drug restraint (medication administered against the explicit will of the patient)[6]. In this sense, MR has been associated with physical and psychological sequelae[3,7] in patients[8] and staff[9].

Many efforts have been made to reduce the use of MR and restrictive measures in general, as evidenced by the numerous legal, ethical, and clinical regulations and/or recommendations that have been developed[10,11]. Nevertheless, MR remains widely used in acute psychiatric care settings throughout Europe, although with marked international variation[12]. According to the European Evaluation of Coercion in Psychiatry and Harmonization of Best Clinical Practice[12], which evaluated and compared the use of restrictive measures in inpatient psychiatric centres in 10 European countries, the percentage of patients subjected to MR in those countries varied widely, ranging from 15% to 55% depending on the country (37% in Spain). This variability is highly influenced by legal, social, and cultural factors[13]. However, given that substantial variation has also been observed within countries, it seems clear that other factors play an important role in the use of MR[9]. The application of MR may also be influenced by variables related to the patient, the staff or the ward. According to some studies, the main determinants for MR are patient-related, including sociodemographic characteristics (age, sex, ethnicity, and employment, housing, and educational status)[14,15] or directly related to the mental disorder (*e.g.*, diagnosis, symptom severity, level of aggression, and recurrence of hospitalization) [15]. Nevertheless, there is some disagreement among these studies with regards to these determinants.

Few studies have evaluated the characteristics and determinants of the duration of MR episodes in psychiatry. Moreover, it is not known whether the reasons for the use of MR are related to the duration. In addition, epidemiological data show that the duration of MR varies greatly, ranging from 4.5 to 1182 h in one study[10].

The available data suggest that there are large differences in the proportion of patients subjected to MR and in the duration of restraint episodes, but the reasons for these discrepancies are still not clear. Given the consequences associated with the use of MR, it is essential to ascertain the underlying mechanisms that lead to MR and prolonged episodes, in order to develop strategies to minimize both the use and duration of MR.

In this context, the objective of the present study was to determine the proportion of patients subjected to mechanical restraint and the duration of these episodes in two acute psychiatric care units in our hospital system. We also aimed to identify the determinants of MR and their duration.

MATERIALS AND METHODS

This was a descriptive study involving a sample of patients admitted to two acute psychiatry hospitalization units (Hospital del Mar and the Dr. Emili Mira Center) at the Parc de Salut Mar (PSMar) in Barcelona from January 1, 2018 to December 31, 2018. The project was approved by the ethics committee at the PSMar (CEIC PSMAR).

Assessment

We determined the percentage of patients admitted to these centres in the year 2018 who were subjected to MR and the duration of these episodes. For the analysis, we considered only the first episode of MR. For patients readmitted during the study period, only the first admission was included.

The following cases were excluded from the analysis: abdominal MR in a bed or chair due to risk of falls, gait instability, or risk of removing life support systems. All data related to the MR episodes were consecutively registered, according to institutional restraint protocols, by staff members (nurses and/or psychiatrists), and incorporated into the patients' medical records. The date and time of day of the incident were recorded. However, some cases were registered several hours after the episode. Since the computer system does not permit any changes in the time or date, we reviewed the medical records of all restrained patients to verify the exact time and duration of the episode. During this review, we also determined whether a language barrier was present. Age, sex, psychiatric diagnoses, and place of birth at the time of restraint were obtained from the medical records. We checked the place of birth to differentiate between non-native and native-born patients in order to include this as a study variable (*i.e.*, potential cultural barrier). The diagnoses were recorded according to the ICD-10 classification and classified into four groups: (1) psychotic disorders (all types of schizophrenia, schizoaffective disorders, manic disorders, and bipolar disorders in manic phase); (2) depressive disorders (including bipolar disorders in depressive phase); (3) substance abuse disorders (SAD); and (4) other mental disorders (anxiety disorders, obsessive compulsive disorders, borderline personality disorders,

Alzheimer's, dementia, anorexia nervosa, among others).

Statistical analysis

Data were analyzed using the IBM-SPSS statistical software, v. 20.0 for Mac. The Kolmogorv-Smirnov test was applied to assess the distribution normality of the variables. Two variables - age and hours of restraint - were not normally distributed. Consequently, we performed a logarithmic transformation, but the distribution remained non-normal. Thus, the raw scores for these variables were used in subsequent analyses.

Univariate analyses were performed to assess differences between those patients who underwent MR and those who did not. The χ^2 test was used to compare the categorical data (sex, diagnosis, language barrier, and cultural barrier). The Mann-Whitney *U* test was performed to assess the role of age (non-normal distribution).

A binary logistic regression analysis was carried out using the "ENTER" method to examine the factors independently associated with MR. In this analysis, MR was the dependent variable and the independent variables were sex, age, diagnosis, and language barrier. For the multivariate analyses, we omitted the cultural barrier due to collinearity problems. The reference diagnostic group was "psychotic disorders".

Another univariate analysis was performed to determine the effect of the various study variables on hours of MR. Spearman's correlation was performed for quantitative variables, the Kruskal-Wallis test for categorical variables with more than one category, and the Mann-Whitney *U* test for categorical variables with two categories. Next, a multiple linear regression analysis was performed ("ENTER" method) to determine the variables independently associated with hours of restraint. In that analysis, the dependent variable was hours of restraint while the independent variables were sex, age, diagnosis, and language barrier.

RESULTS

A total of 474 patients were hospitalized during the study period. Of these, 129 required MR. Ten cases were excluded from the study because MR was applied due to the risk of falls or to start vital system support. Thus, the final sample consisted of 464 patients, 119 of whom were subjected to MR. The sample characteristics are described in Table 1, together with the results of the univariate analysis for MR.

On the univariate analysis, the median age in the MR group was significantly lower than in the non-MR group: ($P = 0.005$; $Z = 2.80$). Patients with a language barrier ($P < 0.0001$; $\chi^2 = 15.06$) or cultural barrier ($P = 0.005$; $\chi^2 = 7.76$) were more likely to be physically restrained than native-born patients. Finally, the diagnostic category was significantly associated with the use of MR ($P < 0.0001$; $\chi^2 = 18.41$) (Table 1).

On the binary logistic regression, the presence of a language barrier was associated with a significant higher risk of MR [Odds radio (OR) = 2.13; 95%CI: 1.2-3.7; $P = 0.007$] and the diagnosis was also a significant determinant of MR. Patients diagnosed with depressive disorder (OR = 0.22; 95%CI: 0.06-0.62; $P = 0.005$) and "other" diagnoses (OR = 0.46; 95%CI: 0.23- 0.93; $P = 0.03$) were significantly less likely to be subjected to MR compared to patients diagnosed with psychotic disorder (Table 2).

Hours of mechanical restraint

The median number of hours of restrain per episode was 16.4 (IQR: 7.98-29.27; $Z = 2.959$). The results of the univariate analysis for hours of MR are shown in Table 3. The univariate analysis showed a significant association between sex and hours of restrain ($P = 0.004$; $Z = -2.856$).

On the multiple linear regression analysis, the only variable significantly associated with hours of restraint was sex, which was longer in men (B = -19.03; 95%CI: -38.06-0.008; $P = 0.05$; $f^2 = 0.03$) (Table 4).

DISCUSSION

The aim of the present study was to determine the proportion of patients subjected to MR and the duration of each episode at our institution during the year 2018. We also sought to identify the main factors associated with the use and duration of MR. During the study period, 25.6% of patients were subjected to MR, with a median duration of 16.4 hours per episode. After controlling for possible confounding factors, the determ-

Table 1 Demographic and clinical characteristics of the study sample according to use of mechanical restraint (univariate analysis), *n* (%)

	n (%)	Without MR	With MR	*Z*, χ^2	*P* value
Age (Median/IQR)	42 (30-53)	44 (31-56)	39 (28-48)	(Z) 2.801	0.005
Sex				1.124	0.289
Male	234 (50.4)	169 (72.2)	65 (27.8)		
Female	230 (49.6)	176 (76.5)	54 (23.5)		
Diagnosis				18.414	0.000
Psychotic disorder	318 (68.5)	219 (68.9)	99 (31.1)		
Depressive disorder	55 (11.9)	51 (92.7)	4 (7.3)		
SAD	21 (4.5)	16 (76.2)	5 (23.8)		
Others	70 (15.1)	59 (84.3)	11 (15.7)		
Language barrier				15.058	0.000
No	388 (83.6)	302 (77.8)	86 (22.2)		
Yes	76 (16.4)	43 (56.6)	33 (43.4)		
Cultural barrier				7.756	0.005
No	313 (67.5)	245 (78.3)	68 (21.7)		
Yes	151 (32.5)	100 (66.2)	51 (33.8)		

IQR: Interquartile range; SAD: Substance abuse disorders.

Table 2 Binary logistic regression analysis

	Beta	SE	*P* value	OR	95%CI for OR	
					Low	High
Age	-0.011	0.008	0.181	0.989	0.973	1.005
Sex	-0.032	0.229	0.889	0.969	0.619	1.516
Diagnosis			0.008			
Depressive disorder	-1.526	0.545	0.005	0.217	0.075	0.633
SAD	-0.427	0.535	0.425	0.652	0.229	1.861
Others	-0.776	0.358	0.030	0.460	0.228	0.928
Language barrier	0.758	0.281	0.007	2.133	1.229	3.702
Constant	-0.501	0.394	0.204	0.606		

OR: Odds ratio; SAD: Substance abuse disorders.

inants of MR were diagnosis (higher risk in patients with a diagnosis of psychotic disorder) and the presence of a language barrier. Furthermore, male gender was the only variable associated with prolonged MR. The proportion of patients who required MR - approximately one out of every four patients admitted to acute care - was similar to the rates reported in other studies, such as the 24% rate reported in a study carried out in Italy[12] and the 28.8% rate in another study in Spain[16]. However, studies conducted in other regions[10,17-20] have reported substantially lower rates of MR (from 1%-8%), probably because other methods (in addition to mechanical and pharmacological restraint) are used in those regions, such as isolation and, in some cases, the patient is allowed to select the restrictive measure. These differences may also be at least partially attributable to different cultural contexts and regulations governing hospitalization of psychiatric patients and the use of MR. Furthermore, given that high intra-country variability has also been observed in many studies, other

Table 3 Basic demographic and clinical characteristics of the study sample according to median hours of restraint (univariate analysis)

	n (%)	Restraint duration		Statistical	
		Median	IQR	Z, χ^2	*P* value
Age				(*r*) 0.027	0.768
Sex				(Z) - 2.856	0.004
Male	65 (54.6)	19.28	11.30-34.13		
Female	54 (45.4)	12.61	6.53-20.03		
Diagnosis				(χ^2) 6.488	0.090
Psychotic disorder	99 (83.2)	17.48	9.13-29.75		
Depressive disorder	4 (3.4)	5.05	2.92-7.86		
SAD	5 (4.2)	11.77	7.98-18.37		
Others	11 (9.2)	13.10	8.88-28.92		
Language barrier				(Z) - 0.819	0.413
No	86 (72.3)	15.68	7.98-29.27		
Yes	33 (27.7)	18.70	9.70-24.57		

IQR: Interquartile range; Z: Statistical value of *U* of Mann-Whitney; *r*: Spearman's statistical value; SAD: Substance abuse disorders.

Table 4 Multiple linear regression analysis

	B	SE	Beta	*t*	*P* value	95% CI for B	
						Low	High
Age	0.252	0.319	0.080	0.792	0.430	-0.379	0.884
Sex	-19.028	9.601	-0.214	-1.982	0.050	-38.063	0.008
Diagnosis							
Depressive disorder	-24.739	25.780	-0.101	-0.960	0.339	-75.850	26.372
SAD	-11.822	21.032	-0.054	-0.562	0.575	-53.520	29.875
Others	8.074	15.317	0.053	0.527	0.599	-22.294	38.442
Language barrier	-1.353	10.110	-0.014	-0.134	0.894	-21.397	18.691
Constant	30.248	20.105		1.505	0.135	-9.611	70.107

OR: Odds Ratio; SAD: Substance abuse disorders.

non-cultural factors, such as patient-related factors or the type of unit, may also help explain the differences.

After controlling for other variables, we found no association between age and MR. In line with our findings, several other studies have found no association between MR and age[20-23]; by contrast, several other studies have reported a significant association[9,13,17,24]. It is important to emphasize that most of the studies that found an association with age did not control for other variables (*e.g.*, diagnosis), whereas the studies that have reported no significant associations did control for other factors. Given that psychotic disorder is diagnosed more frequently in younger patients (relative to other diagnoses), we hypothesised that the key factor that determines the application of MR in younger patients could be the diagnosis rather than age.

Numerous studies have explored the influence of patient sex on MR, with most not finding any significant differences[15,18,21-23,25], in line with our findings. Nonetheless, some studies have reported an association between MR and male sex[17,20,24], although such findings may be due to the failure to control for other factors. In fact, the univariate analysis in two studies[21,22] revealed significant differences between men and women sex in terms of MR, but this difference was no longer significant after

controlling for other variables. This finding suggests that sex alone is not an independent predictor of MR, which may be more influenced by the psychiatric diagnosis or other variables.

In our study, the diagnosis was independently associated with MR. Specifically, patients diagnosed with a psychotic disorder had a significantly higher risk of MR, a finding that is consistent with multiple studies[12,17,22,26-28] and reviews[9,21]. That said, it is worth noting that several studies have not found any association between psychotic disorder and MR[13,23,29]. Different cultural contexts and the grouping of different psychiatric diagnoses in these studies could help to explain the discrepancies between those studies and ours.

Another factor associated with MR in our study was the presence of a language barrier. Although we initially differentiated between language and cultural barriers (due to the inclusion of non-native patients without a language barrier), we ultimately decided to omit the variable "cultural barrier" due to problems of collinearity, thus including only "language barrier" in the multivariate analysis. Other studies have found that being an immigrant (without specifying the presence of a language barrier or not) is a determinant of MR[25,30,31]. A study conducted in Spain in 2010 found that patients classified as immigrants had a significantly higher MR rate than paired Spanish-born hospitalized patients (81% *vs* 31%, respectively)[32]. In a study conducted in Italy, immigrant patients were more likely to require physical restraint than Italian-born patients[30]. A two-year retrospective analysis[25] found a 21.6% MR rate among patients with an immigration history compared with 12.9% of Norwegian-born patients. However, other studies have not found any differences between immigrants and native-born patients[33]. Communication problems derived from cultural and language differences between professionals and patients could lead to less successful interventions in risk situations.

The median duration of restraint in our study was 16.4 h, which is higher than some other studies[29,34]. This difference could be due the availability of other measures (*e.g.*, isolation) in those other studies/regions. Male sex was the only determining factor of restraint duration, a finding that is consistent with other reports[26,34]. Along these lines, it is worth highlighting a study carried out to assess the emotional reactions of staff to violent behaviour in psychiatric hospitalized patients. Interestingly, that study found that men and women provoked different reactions among staff members[35], suggesting that women may be perceived to be less threatening than men, which may partially explain why they are less likely to require prolonged MR.

Limitations

This study has several limitations. The first limitation is the retrospective study design, which did not allow us to explore certain key aspects. For example, we were unable to perform a more detailed clinical assessment of patients prior to and during the restraint period. Another limitation is that we assessed only acute psychiatric patients, who tend to have more severe symptoms, with more frequent and longer lasting episodes of MR. Consequently, the finding reported here may not apply to chronic psychiatric settings.

CONCLUSION

Despite efforts to reduce or eliminate the use of mechanical restraint, the results of this study show that these procedures remain widely used in the acute care units at our hospital. Two variables - a diagnosis of psychotic disorder and the presence of a language barrier - were associated with a greater risk of MR. In addition, male sex was associated with longer restraint periods. It is important to identify the patients most likely to require MR or those likely to require longer duration of MR in order to develop specific protocols to further reduce the use of MR.

ARTICLE HIGHLIGHTS

Research background

The use of mechanical restraint (MR) in hospitalized psychiatric patients remains controversial due to the numerous ethical, legal, and clinical questions associated with this practice. Many efforts have been made to reduce the use of MR. Nevertheless, it remains widely used in acute psychiatric care settings throughout Europe.

Research motivation

It's essential to identify the patients most likely to require MR or those likely to require a more prolonged duration of MR.

Research objectives

The main objective is to determine the proportion of patients subjected to MR and the duration thereof in two acute care psychiatric units. Secondly, to identify the variables associated with the use and duration of MR.

Research methods

Descriptive study of all patients admitted to the acute psychiatric units at the Parc de Salut Mar. The number and percentage of patients subjected to MR and the duration of each episode were assessed. Multivariate analyses were performed to evaluate the determinants of MR and its course.

Research results

The results show that the use of MR is very frequent. The diagnosis of psychotic disorder and the presence of a language barrier were associated with a greater risk of MR. The male sex was associated with longer restraint periods

Research conclusions

Despite efforts to reduce or eliminate the use of MR, the results of this study show that these procedures remain widely used in the acute care units at our hospital. Its determining factors are the psychotic disorder and the language barrier. The factors of a prolonged MR is the male sex.

Research perspectives

It is important to develop specific protocols to further reduce the use of MR.

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World J Psychiatr 2021 October 19; 11(10): 864-875

DOI: 10.5498/wjp.v11.i10.864

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

What factors explain anger and mental health during the COVID-19 pandemic? The case of Israeli society

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Author contributions: Braun-Lewensohn O wrote the manuscript, ran, and analyzed the data; Abu-Kaf S and Kalagy T contributed to writing and analyzing the data; all authors contributed to the article and approved the submitted version.

Supported by the BGU COVID-19 CORONA CHALLENGE.

Institutional review board statement: The study is ethically approved, No. 2020-08.

Informed consent statement: Signed informed consent statement was obtained from the participants.

Conflict-of-interest statement: There is no conflict of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution

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Abstract

BACKGROUND

What factors affected the levels of anger and emotional distress experienced during the coronavirus disease 2019 (COVID-19) pandemic? We hypothesized that (1) sociodemographic factors and resiliency factors would partially explain psychological distress and anger, with stronger resiliency associated with lower levels of distress and anger; (2) women would report more trust in national leadership, as well as more psychological problems; (3) individuals of low socioeconomic status would report less resiliency, less trust in national leadership, and greater distress than individuals of higher socioeconomic status; and (4) hope would mediate the relationships between the other resiliency factors and both anger and distress.

AIM

To explore whether community resilience, hope, and trust in leaders were associated with lower levels of anger and emotional distress during the COVID-19 pandemic.

METHODS

For this observational study, data were gathered in Israel during the second wave of the COVID-19 pandemic, just before the Jewish New Year (mid-September 2020), as a second lockdown was announced. Data were gathered from 636 Israeli adults, who were recruited by the Midgam research panel. The participants filled out self-reported questionnaires including one on state anger, the Brief Symptom Inventory as a measure of mental-health problems (*i.e.*, somatization, depression, and anxiety), and questionnaires about trust in the state's leaders, community resilience (CCRAM), and hope as measures of coping resources and resiliency. *t*-

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Manuscript source: Invited manuscript

Specialty type: Psychiatry

Country/Territory of origin: Israel

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 25, 2021
Peer-review started: April 25, 2021
First decision: July 14, 2021
Revised: July 20, 2021
Accepted: September 8, 2021
Article in press: September 8, 2021
Published online: October 19, 2021

P-Reviewer: Mukherjee M, Saha S
S-Editor: Wu YXJ
L-Editor: A
P-Editor: Li X

tests were used to explore differences between men and women and between those of lower and higher socioeconomic status. A hierarchical multiple regression analysis was then used to examine whether and how the sociodemographic and resiliency variables explained state anger and psychological distress. A Sobel test was used to evaluate the possible effects of hope on community resilience and trust in leadership in the context of both distress and anger.

RESULTS
Our results revealed differences between women and men in terms of anger and mental-health problems, but not in terms of coping resources. Women reported higher levels of both anger and mental-health problems. Participants of lower socioeconomic status reported more mental-health problems, more anger, and greater trust in the state's leaders; whereas those of higher socioeconomic status reported greater hope. Furthermore, hierarchical multiple regression analyses revealed that the sociodemographic factors of gender, age, and socioeconomic status, as well as community resilience, trust in the state's leaders, and hope explained mental health with a total of 19% of the variance and anger with a total of 33% of the variance. The Sobel tests showed that hope mediated the relationships between community resilience and mental health ($z = 3.46$, $P < 0.001$), community resilience and anger ($z = 2.90$, $P < 0.01$), and trust in leaders and anger ($z = 3.26$, $P < 0.01$), but did not affect the relationship between trust in leaders and mental health ($z = 1.53$, $P > 0.05$).

CONCLUSION
Personal and communal factors affect psychological distress. Personal resilience is an important factor that should be strengthened throughout life. Trust in leadership is important for citizens' mental health.

Key Words: Community resilience; Hope; Trust in government; Anger; Mental health; Pandemic

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Core Tip: The aim of this study was to explore whether community resilience, hope, and trust in leaders reduced anger and emotional distress during the coronavirus disease 2019 pandemic. Data were gathered from 636 Israeli adults. The participants filled out self-reported questionnaires including one on state anger, a measure of mental-health problems, and questionnaires about trust in the state's leaders, community resilience, and hope. Our results showed that personal and communal factors play significant roles in reducing psychological distress. This study confirms that personal resilience is an important factor that should be strengthened throughout life. Trust in leadership is important for citizen's mental health.

Citation: Braun-Lewensohn O, Abu-Kaf S, Kalagy T. What factors explain anger and mental health during the COVID-19 pandemic? The case of Israeli society. *World J Psychiatr* 2021; 11(10): 864-875
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/864.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.864

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has led governments around the world to impose lockdowns, which have ranged in duration from several weeks to several months. In Israel, the first lockdown began in March 2020 and continued until May 2020. As the country exited that lockdown, citizens felt that normal life had returned and governmental orders to minimize gatherings were not enforced. Schools opened in early September, with students in isolated groups (capsules). By mid-September, a second wave had arrived and, just before the Jewish New Year, the

government announced a second lockdown, with restrictions that were more severe than those imposed during the first lockdown.

Against the backdrop of the second wave of the epidemic and the second lockdown, the present study aimed to explore communal resources and personal resources, community resilience, trust in the country's leaders, and hope as potential resiliency factors capable of reducing mental-health problems and feelings of anger during this difficult period. We wanted to examine the above-mentioned resiliency and emotional and psychological distress variables among Israeli adults. We compared women and men, as well as individuals of relatively high and low socioeconomic status, to try to understand which of the potential resiliency factors could explain mental-health problems and feelings of anger in this context.

Literature review

Community resiliency: It is important that studies of individuals during a collective crisis take into account the ecological context[1,2], such as different aspects of the communities in which individuals live. Community resilience includes community readiness and preparedness for such events, as well as social cohesion, social support, and social ties and commitments within the community[3-5]. Community resilience and wellness are derived from different capacities, which are dynamic and which must be strengthened and preserved. The current study is focused on the role of community resilience during a pandemic and its association with other resiliency factors in helping individuals to cope during times of epidemics and lockdowns.

Trust in the country's leaders

Faced with the great deal of uncertainty surrounding this novel coronavirus, the public has had to rely on various authorities, such as political leaders and governments, for information and guidance[6]. Trust or confidence in one's country's leaders might serve as an important factor protecting individuals from mental-health problems and feelings of anger during the COVID-19 pandemic.

Indeed, citizens' trust in governmental institutions has been crucial for fostering willing compliance with regulations designed to limit the COVID-19 pandemic[7]. Furthermore, citizens' trust in governmental leadership has helped countries to recover fairly well from the pandemic; countries whose citizens have greater trust in governmental figures and institutions have reported fewer health, psychological, and/or economic problems[8].

Hope

Hope for the future helps us to cope effectively with challenges. It helps individuals to view all of their options and to examine sources of personal strength, by relating to the future instead of focusing on the past[9]. Hope involves emotional elements of expectation, as well as cognition (including deduction) to pursue new ideas and solutions[10,11]. Some researchers have viewed hope as a positive attitude toward life and the ability to hold optimistic views[12-14]. Jacoby and Goldzweig[15] emphasized the emotional component of hope that exists alongside the cognitive component[15]. It is widely agreed that hope is an important resiliency factor that helps individuals to cope and that high levels of hope facilitate well-being in various stressful situations (*e.g.*,[16]).

Indeed, hope has been found to lead to positive outcomes even during a pandemic [17,18]. Thus, in this study, we explored and examined the global concept of hope as a resiliency factor that might aid in reducing mental-health problems and feelings of anger. This study was designed to explore the concept of hope as a potential mediator between community resilience or trust in leadership and mental-health outcomes.

Mental health and anger

Stress has cognitive, emotional, physical/somatic, and social aspects[19]. Research has shown that individuals who are exposed to stressful situations, including the COVID-19 pandemic and the lockdowns and curfews that were imposed in attempts to control that pandemic, tend to be especially vulnerable to developing mental-health problems and anger[20-23]. In summary, those who report higher hopes, stronger community resilience, and more trust also report fewer mental-health symptoms and lower levels of anger[16,24-26].

Gender: No significant gender differences have been found for hope or community resilience[27-29]. However, women have been found to express greater trust in government and leaders[30]. In general, women report more mental-health problems

and feelings of anger than men do and this has held true during the COVID-19 pandemic[31,32].

Age: Older individuals tend to express more community responsibility and resiliency and more trust than their younger counterparts[29,30]. Younger people tend to report higher levels of hope[33], as well as more mental-health problems[32,34].

Socio-economic status: Low socio-economic status (SES) has been found to be associated with lower levels of hope[35] and less confidence and trust in officials, systems, and governments[36]; whereas higher SES has been found to be associated with higher levels of hope[35]. Additionally, low-SES individuals tend to report more mental-health problems than their high-SES counterparts in various stressful situations, including the COVID-19 pandemic[37].

In accordance with the literature review and the aims of the study, several research questions and hypotheses were formulated: (1) Are there differences between men and women in terms of the study variables, namely, hope, trust in leaders, community resilience, mental-health problems, and anger? We expected to find that women report more trust in the country's leaders and more psychological problems (*e.g.*,[30,31]). We did not expect to find any gender differences in the various resiliency factors (*e.g.*,[29]); and (2) Are there differences between individuals of different socioeconomic levels in terms of the study variables, namely, hope, trust in leaders, community resilience, mental-health problems, and anger? Lower-SES individuals were expected to report weaker resiliency than their higher-SES counterparts[35] and to have less trust in their leaders[36]. We also expected that they would report higher levels of psychological distress[37].

To what extent do sociodemographic variables (*i.e.*, gender, age, and SES) and the resiliency factors of hope, community resilience, and trust in leaders explain psychological distress and feelings of anger? We expected that the various sociodemographic factors and the different resiliency variables would contribute to the explanations of both psychological distress and anger. We also expected that stronger resiliency factors would be associated with lower levels of psychological distress and lower levels of anger[16,24].

Does the personal resource of hope mediate the relationships between community resilience or trust in leaders and mental-health problems or feelings of anger? We expected that hope would mediate those relationships[38].

MATERIALS AND METHODS

Participants

Data were gathered from 636 Israeli adults aged 18-70 years old (mean ± SD: 37.14 ± 12.63). The sociodemographic data are presented in Table 1.

Procedure

All of the ethical guidelines applicable to this study were followed. The study was approved by the Human Subjects Ethics Committee of the Conflict Management and Resolution Program at Ben-Gurion University of the Negev (Approved Ethics Form No. 2020-008). Participants completed self-report questionnaires in mid-September 2020, just before the Jewish New Year, as a second lockdown was being announced and approximately six months after the start of the COVID-19 pandemic. The participants were recruited by the Midgam panel (https://www.midgampanel.com/) and were informed that the researchers were interested in their experiences. They were also informed that their participation was voluntary and anonymous and that they were free to withdraw their participation for any reason at any time during the questionnaire procedure.

Measures

Demographics: Participants were asked to report their gender, age, and SES. SES was measured by one question in which participants were presented with the average salary in Israel and asked whether they earned less than that amount or that amount or higher. They were also asked to report their marital status, whether they had any children, and their type of employment (*i.e.*, full-time, part-time, or not employed at all).

Table 1 Frequencies and prevalence of the various sociodemographic variables

Variable	*n*	Prevalence (%)
Gender		
Women	342	53.8
Men	294	46.2
Socioeconomic status		
Below average salary	397	56.6
Average/above average salary	239	34
Current work		
Full time	408	64.2
Part time	79	12.4
No work at all	149	23.4
Family status		
Single	202	31.8
Married	397	62.4
Divorced	35	5.5
Widowed	2	0.3
Children		
Yes	407	64
No	229	36

Conjoint community resilience assessment measure: We used the short version of this scale, which includes 10 items that are each scored on a 5-point Likert-type scale ranging from 1 (do not agree at all) to 5 (definitely agree). The scale is constructed to assess conjoint community resilience assessment measure and to facilitate the estimation of an overall community-resiliency score. It also detects the strength of five important constructs of community functioning following a disaster: Leadership, Collective Efficacy, Preparedness, Place Attachment, and Social Trust. Examples of items are: "I feel that I belong to the place where I live; I believe that my community has the ability to overcome a crisis." The Cronbach's alpha coefficient for the entire scale was $\alpha = 0.91$.

The Conjoint Community Resiliency Assessment Collaboration (CCRAC) is coordinated by Limor Aharonson-Daniel and Mooli Lahad[1]. Partners are: Bruria Adini, Miriam Billig, Orna Braun-Lewensohn, Daphna Canneti, Odeya Cohen, Paula Feder-Bubis, Avi Israeli, Shaul Kimhi, Dima Leykin, Sabina Lissitsa, Yochanan Peres, Carmit Rappaport, Avi Sender, Shifra Sagy, and Michal Shamai.

Trust in the nation's leaders: This questionnaire included six questions that were each answered on a scale of 1 (not at all) to 5 (very much). This questionnaire was designed specifically for the present study, to try to evaluate the extent to which the Israel public believed that its leaders were making the right decisions during the pandemic. Participants were asked to evaluate the government as a whole, minsters, and members of parliament, in terms of how much they each cared and worked for the citizens in the country. Examples of items: "You can trust the government; The government does not spend money on the right things; The government is attentive to the public; The members of the parliament are attentive to the public." The mean was computed and the reliability was $\alpha = 0.84$.

Hope[15]: We used the 18-item, short version of a hope questionnaire. Each item was scored on a Likert scale ranging from 1 (do not agree at all) to 4 (totally agree). The global scale of hope used for the current study is built out of three subscales: Interpersonal Hope, Intrapersonal Hope, and Transpersonal Hope. Examples of items: "I draw strength from the relationships in my life; At difficult times in my life, I trust that I will be able to get myself out of the difficult situations I face; I have faith, which

gives me a sense of comfort". In the present study, the mean of the 18 items was computed. The Cronbach's alpha coefficient was α = 0.91.

State anger[39]: This scale consists of six items related to different aspects of anger. The participants were asked to respond to the items using a 4-point Likert scale (1–almost never; 4–almost always). Examples of items: "I am angry; I want to scream at someone; I feel frustrated". The mean scores were used and the Cronbach's alpha coefficient was α = 0.89.

Brief Symptom Inventory[40]: We used the short version of this inventory, which is comprised of 18 items that are each rated on a 5-point Likert scale (0–not at all; 4–very much). This questionnaire examines three areas of psychological and psychiatric problems: somatization, depression, and anxiety; which can be combined into one scale, namely, the Global Severity Index. Examples of items: "To what extent have you felt faint or experienced dizziness? To what extent have you suffered from a feeling of stress? To what extent have you suffered from a feeling of depression?" The reliabilities of the short version of the questionnaire and its three subscales have been reported to be good[41]. The Cronbach's alpha coefficient for the Global Severity Index was α = 0.88.

Data analyses

First, *t*-tests for independent samples were computed to explore differences between men and women and between those of lower and higher SES, in terms of all of the study variables. Secondly, a hierarchical multiple regression analysis was conducted to evaluate the explanations of the two dependent variables, state anger and the Global Severity Index, by the sociodemographic, resiliency, and resource variables. Finally, we used a Sobel test to evaluate the possible effects of hope on community resilience and trust in leaders in the context of both mental-health problems and feelings of anger.

RESULTS

Differences were found between men and women, in terms of the outcome variables. The women suffered from more severe psychological problems and reported higher levels of state anger, confirming our hypothesis. No gender differences were found in terms of any of the coping resources. Results are presented in Table 2.

As for the hypothesis regarding SES, differences were found in terms of all of the variables, except for community resiliency. Those who belonged to the lower-SES group reported more trust in the country's leaders, greater anger, and more severe psychological distress; whereas those from the higher-SES group reported higher hopes. Results are presented in Table 3.

Our third hypothesis related to the explanation of the dependent variables state anger and Global Severity Index (psychological distress) by the various sociodemographic factors of SES, age, and gender, and the resiliency factors of community resilience, trust in leaders, and hope. The overall explanation of state anger by the various variables was 19%. Those variables explained 33% of the scores on the global severity index of psychological distress. The results (presented in Table 4) show that the sociodemographic variables played different roles in the explanations of state anger and psychological distress. Each of those variables played a significant role in the context of psychological distress, but only gender had a significant effect on anger. All of the resiliency factors played significant roles in explaining each of the two dependent variables.

Finally, a Sobel test was run to examine the variable of hope as potential mediator of the relationships between community resilience or trust in leaders and mental-health problems or feelings of anger. Our results show that hope mediated the relationships between community resilience and mental health ($z = 3.46$, $P < 0.001$), community resilience and anger ($z = 2.90$, $P < 0.01$), and trust in leaders and anger ($z = 3.26$, $P < 0.01$), but did not affect the relationship between trust in leaders and mental health ($z = 1.53$, $P > 0.05$). Thus, it seems that, overall, the individual resiliency factor of hope was the most important factor protecting individuals from mental-health problems and feelings of anger during this pandemic.

Table 2 Differences between men and women in terms of the main variables

	Women, *n* = 324	Men, *n* = 281	*t*
CCRAM (1-5)	3.23 ± 0.97	3.16 ± 0.84	0.94
Trust in leaders (1-5)	2.14 ± 0.85	2.15 ± 0.90	-0.11
Hope (1-4)	3.21 ± 0.55	3.17 ± 0.53	0.63
State anger (1-4)	1.97 ± 0.71	1.81 ± 0.70	2.68[b]
Global severity index (0-2)	1.01 ± 0.87	0.68 ± 0.62	5.56[c]

[b]$P < 0.01$.

[c]$P < 0.001$. Date is presented as mean ± SD. CCRAM: Conjoint community resilience assessment measure.

Table 3 Differences between the socio-economic status groups in terms of the main variables

	Low SES, *n* = 378	Average/high SES, *n* = 227	*t*
CCRAM (1-5)	3.18 ± 0.95	3.23 ± 0.86	-0.58
Trust in leaders (1-5)	2.23 ± 0.88	2.01 ± 0.85	2.98[b]
Hope (1-4)	3.15 ± 0.56	3.26 ± 0.49	-2.33[a]
State anger (1-4)	1.94 ± 0.72	1.82 ± 0.71	2.08[a]
Global severity index (0-2)	0.97 ± 0.81	0.67 ± 0.70	4.65[c]

[a]$P < 0.05$.

[b]$P < 0.01$.

[c]$P < 0.001$. Date is presented as mean ± SD. SES: Socio-economic status; CCRAM: Conjoint community resilience assessment measure.

DISCUSSION

The aim of this study was to examine Israeli adults' resiliency factors against the backdrop of a second lockdown during the COVID-19 pandemic. In our study, the women reported more psychological distress than the men. This is similar to the findings of other studies of different stressful situations around the world (*e.g.*,[31]). It remains unclear whether women feel that they have more social permission to report distress or whether they objectively feel more distress. In accordance with our hypothesis, women also reported higher levels of anger. It could be that the traditional roles of women in terms of home maintenance and child care, as well the fact that more women than men lost their jobs during this period[42] put an extra burden on women during the COVID-19 pandemic and, as a result, they felt more anger. No gender differences were found for any of the examined resiliency factors. However, trust in the country's leaders was low for both men and women, indicating that the Israeli public did not think that the prime minister, the government, and the members of parliament were taking good care of the public and pursuing their welfare during the difficult, prolonged situation of the pandemic.

The second research question related to differences between individuals with average/high and low SES, in terms of the different study variables. Most of the study's results confirm the results of other studies, such as low-SES individuals reporting more mental-health problems[37] and lower levels of resiliency factors, such as hope, among low-SES populations[35]. However, although all of the participants reported low levels of trust in the country's leaders, our finding that lower-SES individuals reported higher levels of trust in the country's leaders contradicts previous studies[36]. It should be noted that, in Israel, a majority of supporters of the government during the time of the study were members of low-SES groups, namely, people who live in the periphery of the country, those with traditional beliefs, and Ultra-Orthodox Jews. These individuals had supported that government and the then-prime minister for more than a decade[43]. Moreover, they had maintained that support despite criticism from numerous directions regarding the performance of the country's political leaders during this pandemic.

Table 4 Results of hierarchical multiple-regression analysis predicting state anger and psychological distress, as measured by the global severity index

	State anger			GSI		
	R^2	β	*t*	R^2	β	*t*
Step 1	0.02			0.11		
SES		-0.06	-1.35		-0.11	-2.62[b]
Age		-0.06	-1.42		-0.21	-5.11[c]
Gender		-0.10	-2.40[a]		-0.20	-4.96[c]
Step 2	0.06			0.08		
SES		-0.06	-1.34		-0.10	-2.38[b]
Age		-0.04	-1.09		-0.19	-4.87[c]
Gender		-0.11	-2.73[b]		-0.21	-5.50[c]
CCRAM		-0.24	-6.05[c]		-0.28	-7.62[c]
Step 3	0.04			0.01		
SES		-0.08	-1.97[a]		-0.11	-2.96[b]
Age		-0.06	-1.34		-0.19	-5.00[c]
Gender		-0.10	-2.63[b]		-0.20	-5.43[c]
CCRAM		-0.18	-4.53[c]		-0.26	-6.72[c]
Trust in leaders		-0.22	-5.33[c]		-0.09	-2.36[a]
Step 4	0.07			0.13		
SES		-0.05	-1.33		-0.08	-2.16[a]
Age		-0.05	-1.30		-0.18	-5.24[c]
Gender		-0.11	-3.02[b]		-0.22	-6.25[c]
CCRAM		-0.08	-2.03[a]		-0.13	-3.47[b]
Trust in leaders		-0.19	-4.85[c]		-0.06	-1.55
Hope		-0.29	-7.33[c]		-0.38	-10.40[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$. GSI: Global severity index; CCRAM: Conjoint community resilience assessment measure; SES: Socio-economic status.

Our main results relate to community resiliency, trust in leaders, and hope, which significantly explained both psychological distress and anger. These results continue a line of studies that have stressed the importance of communal[24] and personal[17] resiliency factors for helping individuals to cope with various ongoing stressful situations, including the current pandemic. In this study, the communal factor was found to be an important protective factor. Local leaders, such as mayors and local council heads, who created different activities to benefit their residents in the fields of education, sports, culture, *etc.* strengthened their residents' resiliency and thereby contributed to their residents' well-being without relying on the national leaders to do so. An additional novel aspect of this study is the introduction of another potential resiliency factor, namely, trust in the country's leaders, which was found to protect and aid in reducing stress and anger. Indeed, this factor was significantly associated with stress and anger. Greater trust was associated with lower levels of distress and fewer feelings of anger. This could be explained by the fact that when one trusts his/her leaders, she/he can be confident that the public is being taken care of and that decisions are being made in the public interest.

Our last question related to the mediating role of hope in the relationships between community resilience or trust in the country's leaders and psychological distress or anger. Hope did indeed mediate these relationships. Hope proved to be the most important and significant factor in reducing stress and anger. As noted in other studies, hope helps individuals to cope well, facilitates well-being, and leads to

positive outcomes in various stressful situations, including a pandemic (*e.g.*,[16-18]).

Study limitations

Information about participants' experiences during the COVID-19 pandemic was provided only by the participants themselves and, therefore, the collected data are subjective. In addition, because we lack baseline information about the rates of psychological distress and resiliency factors among the surveyed individuals prior to the study period, we cannot with certainty ascribe the outcomes solely to the impact of the examined stressful situation.

Strengths

The importance of this study lies in the fact that it is a field study conducted during a stressful situation, which provided a natural laboratory for the investigation of human behavior[44]. Future studies should employ a longitudinal design to examine the nature and direction of the observed relationships, such as the impact of one variable on another.

CONCLUSION

The current study aimed to explore personal and communal resiliency factors, as factors that might reduce anger and emotional distress during the chronic-stress situation of the COVID-19 pandemic. It seems that both personal and communal factors play significant roles in reducing psychological distress. Therefore, it is important for communal leaders to play significant roles in this type of situation. They should play active roles during crises, including epidemics. This study continues a line of studies that have claimed that personal resilience is an important factor that should be strengthened throughout life. Finally, trust in the country's leaders is important for its citizens, not only for their obedience to published guidelines, but also for their mental health and, therefore, leaders around the world should act to facilitate and strengthen such trust. These findings could also be beneficial and useful for counselors and other mental-health professionals.

ARTICLE HIGHLIGHTS

Research background

We aimed to examine community resilience, hope, and trust in leaders as potential contributors with lower levels of anger and emotional distress during the coronavirus disease 2019 (COVID-19) pandemic.

Research motivation

To understand in what ways personal and communal factors as well as trust in leaders affect psychological distress of citizens during health pandemic.

Research objectives

(1) To assess sociodemographic factors and resiliency factors as explanatory factors of psychological distress and anger, with stronger resiliency associated with lower levels of distress and anger; (2) To examine gender differences on trust in national leadership and psychological problems; (3) To examine differences between individuals from socioeconomic status on resiliency, trust in national leadership, and distress; and (4) To explore the mediating role of hope in the relationships between resiliency factors and anger and distress.

Research methods

Data were gathered from 636 Israeli adults. The participants filled out self-reported questionnaires. *t*-tests and hierarchical multiple regression analysis were used to examine the various research questions.

Research results

Differences between women and men were revealed on anger and mental-health problems, but not in terms of coping resources. Individuals of lower socioeconomic status reported more mental-health problems, more anger, and greater trust in the

state's leaders; whereas those of higher socioeconomic status reported greater hope. The sociodemographic factors of gender, age, and socioeconomic status, as well as community resilience, trust in the state's leaders, and hope explained mental health with a total of 19% of the variance and anger with a total of 33% of the variance.

Research conclusions

Personal and communal factors affect psychological distress. Personal resilience is an important factor that should be strengthened throughout life. Trust in leadership is important for citizens' mental health.

Research perspectives

Trust in the country's leaders is important for its citizens, not only for their obedience to published guidelines, but also for their mental health and, therefore, leaders around the world should act to facilitate and strengthen such trust. These findings could also be beneficial and useful for counselors and other mental-health professionals.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 876-896

DOI: 10.5498/wjp.v11.i10.876

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Measures of empathy in children and adolescents: A systematic review of questionnaires

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Author contributions: Masi G and Sesso G contributed to study conception and design; Sesso G and Brancati GE performed the systematic search and drafted the manuscript; Fantozzi P and Inguaggiato E revised the draft and contributed to the interpretation of the data; Milone A and Masi G critically revised the article; all the authors approved the final version of the article to be published.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Empathy has long been considered a multidimensional construct, encompassing cognitive, affective and behavioral domains. Deficits in empathic competences in early childhood contribute to psychopathology, and have been variably implicated in several clinical conditions, such as autism spectrum disorders (ASD) and conduct disorders.

AIM

To identify and describe empirically validated questionnaires assessing empathy in children and adolescents and to provide a summary of related theoretical perspectives on empathy definitional issues.

METHODS

A systematic review of the literature was conducted. Three bibliographic databases were searched. A total of 47 studies were selected for final analysis and 16 distinct measures were identified and described.

RESULTS

Questionable to excellent levels of internal consistency were observed, while few studies assessed test–retest reliability. Although construct definitions only partially overlapped, affective and cognitive domains of empathy were the commonest internal factors that were often separately evaluated. New facets of the construct (*i.e.*, somatic empathy and sympathy) and specific clinical populations (*i.e.*, ASD) could be specifically addressed through more recent instruments.

CONCLUSION

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Manuscript source: Invited manuscript

Specialty type: Psychology

Country/Territory of origin: Italy

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 16, 2021
Peer-review started: February 16, 2021
First decision: May 13, 2021
Revised: May 15, 2021
Accepted: August 19, 2021
Article in press: August 19, 2021
Published online: October 19, 2021

P-Reviewer: Garcia-Campayo J
S-Editor: Wu YXJ
L-Editor: Kerr C
P-Editor: Guo X

The combination of different assessment methods is recommended in order to foresee further improvements in this field and try to overcome the problem of limited convergence with more objective measures.

Key Words: Empathy; Assessment; Child; Adolescent; Autistic disorder; Conduct disorder

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Core tip: Measures of empathy in children and adolescents constitute useful clinical tools for evaluating impairments in empathic competences and social skills within neurodevelopmental disorders and psychiatric conditions. However, the choice of the instrument to use should clearly vary, depending on the setting and the object of study. The present review could be useful to clinicians and researchers to allow a direct comparison of the available measures and identify strengths and limitations of each one depending on different purposes.

Citation: Sesso G, Brancati GE, Fantozzi P, Inguaggiato E, Milone A, Masi G. Measures of empathy in children and adolescents: A systematic review of questionnaires. *World J Psychiatr* 2021; 11(10): 876-896
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/876.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.876

INTRODUCTION

In the 19th century, the term *Einfühlung* (*ein*- 'into' + *Fühlung* 'feeling') was first coined by Vischer to mean humans' spontaneous projection of psychic feelings into people and things they perceive[1]. Later, the term empathy (from Greek empatheia: *em*- 'in' + *pathos* 'feeling') was suggested by Titchener as a process of humanizing objects and feeling ourselves into them[2]. Psychoanalysis from its beginning was attracted by the concept, viewed as the process of "feeling in the guise" of another person to better understand how therapy works[3]. Since then, many other disciplines of psychology demonstrated a broad interest in empathy[4], and the construct has proved itself as highly relevant to psychiatric research and clinical practice with patients affected by autism spectrum disorders (ASD) or psychopathy[5].

The acquisition of empathy is considered an essential component of moral development, and empirical relationships between many forms of prosocial behavior and empathy have been demonstrated. Indeed, empathy plays an important role in the development of social competence[6]. Adolescents with higher levels of trait empathy exhibit more prosocial and altruistic behavior, whereas adolescents with lower levels of empathy have been shown to be more aggressive. Deficits in empathic competences in early childhood contribute to psychopathology later in life, and have been implicated in the development of antisocial behaviors, bullying, aggression, sexual offending, and serious violent crime. Iindividuals who share and comprehend another's distress, which occurs as a result of their own aggressive or antisocial behavior, may be less inclined to continue with this behavior or act in an antisocial or aggressive manner in the future[6]. Reduced empathy is also observed in children with conduct disorder (CD) and callous–unemotional traits[7-9]. However, few studies have distinguished between proactive and reactive aggression; the former of which may be more strongly associated to low empathy levels, thus often resulting in a nonsignificant relationship between empathy and overall aggression.

Empathy deficits have also been implicated in several other neurodevelopmental disorders, among which autism is one of the most studied. The so-called extreme male brain theory of autism[10,11] proposes that individuals with ASD show reduced empathy and perform worse on empathy-related tasks that normally give rise to female superiority, especially reflecting a specific cognitive empathy impairment. Additionally, novel hypotheses that imply empathy deficits in different mental disorders have emerged in the last decade. Among such conditions, attention deficit and hyperactivity disorder[12-15] and anorexia nervosa[16-18] revealed empathic defects by means of both self- and parent-reported questionnaires.

Despite its relevance, the construct of empathy has posed noteworthy definitional issues that are still under debate. For instance, eight different conceptualizations of empathy have been reported by Batson[19]. Empathy has been first identified as a primarily affective phenomenon, referring to the immediate experience of the emotions of another person[20]. A definition of empathy, as a primarily cognitive construct, has been subsequently proposed, referring to the intellectual understanding of another's experience[21]. However, since the initial differentiation of its instinctive and intellectualized facets in the 18th and 19th centuries, empathy has been considered a complex multidimensional concept, including both cognitive and affective facets, or manifesting either in the cognitive or the affective domain, depending on the situation [22]. Indeed, empathy has been conceptualized as a superordinate category with subclasses of phenomena sharing the same mechanism, including emotional contagion, sympathy, cognitive empathy, helping behavior, and empathic perspective taking[23,24]. Decety and Jackson[25] identified four subjectively experienced components of empathy, *i.e.*, affective sharing, self-awareness, perspective taking, and emotion regulation. A 3D model has also been proposed, including the affective response, the cognitive processing, and the conscious decision making to undertake an empathic or prosocial action[26].

Although empirical literature has not always consistently distinguished between these subtypes of empathy, neurobiological research has indeed suggested that these components reflect independent processes and are governed by separate brain systems [27]. Prefrontal circuits are believed to facilitate empathic responses through enhancing working memory and improving the ability to assess likely outcomes[23]. In addition, anterior insula and anterior cingulate cortex are activated during the empathic experience of others' pain, while the medial dorsal and orbitofrontal cortex and the right temporoparietal junction are activated by empathy appraisals[27]. Converging evidence from several studies shows that the inferior frontal gyrus and the inferior parietal lobule are necessary for affective empathy, while the ventromedial prefrontal cortex, temporoparietal junction, and the medial temporal lobe are key regions for cognitive empathy[28]. Intriguingly, correlates of empathy subtypes have been measured using several physiological measures, such as electromyography (EMG), somatosensory event-related potentials, and transcranial-magnetic-stimulation-induced motor-evoked potentials[29].

Several approaches have been used to measure empathy, with the first instruments dating back to the 1940s, *e.g.*, Dymond's Scale for the Measurement of Empathic Ability[30]. From the 1980s, physiological measurements, such as skin conductance and heart rate, were increasingly being used and, later, empathy measurement has been influenced by the development of social–cognitive neuroscience. Empathy measures have been previously generally reviewed elsewhere[22,31,32]. In particular, Neumann *et al*[33] provided a brief and succinct review of empathy measures, distinguishing behavioral measures (including reactions to strips or picture stimuli), neurophysiological approaches (*e.g.*, functional magnetic resonance imaging, facial EMG, electroencephalography and evoked related potentials) and self-report questionnaires. Among the last category, the authors included eight measures, of which only three were validated in children and adolescents [Feeling and Thinking (F&T) scale, Basic Empathy Scale (BES), Griffith empathy measure (GEM)]; further, one behavioral measure (Kids' Empathetic Development Scale) was specifically intended to be administered to children.

Miller and Eisenberg[34] first systematically reviewed studies correlating empathy and behavior in children and adolescents, subdividing them by the mode of assessing empathy. They identified four methods traditionally used to assess empathy in children. These include picture and/or story methods, in which probands respond to hypothetical stories; experimental induction procedures, designed to elicit empathic responses; facial affect and/or gestural reactions to others' emotions, as depicted in films or picture stimuli; and self-, parent- or teacher-report questionnaires. Each of these methods has advantages and disadvantages[35]. While most real-life social and interpersonal situations are complex and dynamic, and involve multiple players, most test scenarios rely on very simple two-person interactions. Moreover, infants and young children respond to others' emotions before developing the ability to express or define an emotion lexicon[34]. Laboratory-based stimuli are expensive, relatively invasive, and not suited for large community studies and clinical diagnostic settings. Facial and gestural responses to empathy-inducing stimuli, as well as physiological measures, also tend to be complicated, usually involving special equipment and time-consuming data processing and analysis. Even though these types of data are relatively independent of social desirability, young children may react to the physiological equipment. In addition, Problems also arise with these measures when

trying to disentangle or distinguish between physiological responses for empathy, sympathy and distress, as there is little observable physiological distinction between them[36,37].

There are substantial problems with using self-report questionnaires of empathy in children[33]. Indeed, young children lack the cognitive and verbal abilities to report on internal states. For older children, their reports of affective empathy and their scores on picture/story indices still do not converge with their prosocial behavior and are heavily affected by demand characteristics. Nonetheless, self-report can be a vital tool for some research questions, with responses reflecting attitudes and likely behavior. The inclusion of a social desirability assessment is also recommended, as children have a tendency to provide socially acceptable answers to please others, which is a major general limitation of self-administered questionnaires, so it would be advisable to complement the evaluation of the construct with other measures and informants[35]. Parent or teacher surveys are relatively unbiased and more cost- and time-efficient, especially when studying young children[35]. Anyway, self- or others-reported questionnaires remain the most common method for structured assessment of the behavioral correlates of empathy both in adults and in children and adolescents. While multimethod approaches are clearly favored in basic research, such approaches are not fully applicable to the clinical context, where both timing and setting often limit the extent of more thorough investigation. In fact, rating scales and questionnaires are essential to clinical evaluation for therapeutic and research purposes.

Clinicians and researchers in the neurodevelopmental field still lack a comprehensive overview of validated questionnaires for measuring empathy. Indeed, a systematic review of studies validating questionnaires that clinically evaluate empathy deficits in the pediatric population was published in French in 2016[38]. However, it was limited to the adolescent population (age 12–18 years) and to the period from January 2002 to December 2012, and it was mainly aimed at assessing the clinical features of empathy deficits. Only three validated instruments, namely the BES, the GEM and the Interpersonal reactivity index (IRI), were selected and described. Given the apparent lack of exhaustive and thorough reviews on the topic, published in English, we conducted an updated systematic review of the existing literature on questionnaires assessing empathy validated in children and adolescents. The main goal of our search was to identify the available measures of empathy, and to define how reliable and valid they are. As a consequence, we decided to restrain our search to studies aimed at validating empathy questionnaires (EQ). Psychometric validation of multiple-item scales is an integral and essential part of data analysis, to allow a direct comparison of distinct measures used to assess the same construct. Nevertheless, applied research often do not include psychometric evaluations of the tools, which results in the common use of measures with insufficient proof of validity and reliability and raises concerns on their applicability[39]. Thus, including studies that did not provide a psychometric validation of the used empathy measures would have had little meaning in the present systematic review, whose scope was, among the others, to compare the robustness of each tool. Moreover, since we were interested in identifying the definitions of the construct and the components on which each measurement was based, we provided measures structure comparison with a summary of related theoretical perspectives on empathy definitional issues which are relevant to neurodevelopmental disorders.

MATERIALS AND METHODS

Search

A systematic review of the literature was conducted and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to describe procedures and results[40]. PubMed, Scopus and Web of Science bibliographic database were searched from their date of inception to February 2019. Reference lists of included studies were also carefully searched for relevant citations. The research team discussed and reviewed the results of an initial scoping search. We developed a strategy using four groups of search terms. These were: empathy OR empathic (group 1) AND questionnaire OR measure OR measurement OR scale (group 2) AND child OR children OR adolescent OR youth (group 3) AND validity OR validation (group 4). In summary, the strategy was to include all relevant abstracts relating to groups 1–4. Terms were adapted as necessary for each database. Results were downloaded into Mendeley software. The search included reviews and original studies. If a previous review was found, we searched the reference list to identify and

retrieve the primary studies.

Eligibility criteria

Studies were included if they met the following criteria: Study design: studies aimed at presenting or validating original questionnaires of the psychological construct of empathy, validating their adaptations to other samples or translations into different languages, or further evaluating psychometric properties of these measures.

Comparison: No restriction for comparison groups was applied.

Participants: Children, adolescents and/or young people under 21 years old.

Definition: Any definition of the empathy term was accepted.

Measures: Any questionnaire assessing empathy, including paper-and-pencil or computer-administered measures.

Studies were excluded if they met at least one of the following criteria: (1) the study was not aimed at validating a measure (*e.g.*, assessing a clinical cohort or comparing it with a control population by means of a specific measure); (2) the study was aimed at validating a measure other than a questionnaire (*e.g.*, picture-based tasks or experimental procedures); (3) the validated questionnaire was intended to assess a related psychological construct other than empathy (*e.g.*, social skills, aggressive behaviors, callous–unemotional traits) or to provide diagnostic measures for psychopathy and antisocial personality, ASD and Asperger syndrome, social anxiety; (4) the validated questionnaire was not intended to primarily assess empathy but more general related constructs that only marginally included empathy-related subscales (these measures will be considered in the Discussion); (5) the validation was performed on samples including adults or young adults aged ≥ 21 years; (6) the full-text article was written and published in a language other than English, French, Spanish or Italian (only these languages are well mastered by the authors); and (7) reviews (they will be considered in the Discussion).

Abstract screening

We retrieved 911 abstracts using our search strategy, and 285 were removed as duplicates. Ten additional records were identified through other sources (citations in reference lists of screened papers and reviews). Thus, 626 + 10 abstracts were screened. If a title appeared potentially eligible, but no abstract was available, the full-text article was retrieved. Two researchers (Sesso G and Brancati GE) scanned all titles and abstracts to identify relevant articles for full-text retrieval. Any disagreements were resolved by consensus.

Data collection process

For each study, data on participants and setting, country and language of validation, size, age and gender of the sample and relevant measurements were extracted from full-text papers. For each measure, full name and abbreviation of the scale, number of subscales and items, number of response points for Likert-type scales, identity of responders (self- or parent-reported), empathy definition on which they are based, and data on reliability and validity were also extracted. Finally, data on languages of translation, novel versions or adaptations, and psychometric properties were extracted from full-text papers that were not aimed at presenting or validating original measures.

Synthesis of results

The included studies were heterogeneous in terms of definition and measurement of empathy; hence, we report a narrative synthesis of the findings together with discussion of relevant theoretical background. For each assessment scale we identified psychometric properties from the correspondent paper or from the wider literature. In order to synthesize the articles, identified through our search, we partitioned the papers in four groups: those aimed at presenting or validating original questionnaires; those aimed at validating novel versions or adaptations; those aimed at validating their translations into different languages; and those aimed at further evaluating psychometric properties of validated measures. Original measures were also classified based on validation in infants, preschool children, children and/or adolescents, and as parent- or self-rated.

RESULTS

Study selection and excluded measures

The PRISMA flowchart (Figure 1) shows the process of identification and selection of papers. We excluded 572 records based solely on title or abstract. A total of 64 full-text articles were thoroughly assessed, of which 17 were excluded. The main reasons for exclusion were: the study was aimed at validating a measure other than a questionnaire (n = 4); the validation was performed on samples including adults or young adults ≥ 21 years old (n = 10); or the full-text article was written in a language other than English, French, Spanish or Italian (n = 3).

We excluded measures intended to assess psychological constructs such as aggressive behavior and callous–unemotional traits, or to provide diagnostic clues for psychopathy and antisocial personality, which have been recently reviewed by Masi *et al*[41], and for ASD and Asperger syndrome, for which we refer to the broad available literature on the topic. We extended our search to the entire pediatric population, including infants, preschool children, school-age children and adolescents, but limited it to only paper-and-pencil or computer-administered questionnaires, both self- and parent-report (for instance, we excluded the Young Children's Empathy Measure[42] as it is a vignette-based interview).

Only full-text articles written and published in English, French, Spanish or Italian were retrieved, since these are the only languages that are sufficiently mastered by the authors to fully access the content of the papers. Unfortunately, the Media-Based Empathy Scale[43] was excluded, although being the only existing measure of empathy in the context of media use, since the full-text article was written in German, as well as the Child and Adolescent Forms of the KA–Sİ Empathic Tendency Scale[44, 45], a self-reported questionnaire with affective and cognitive empathy subscales, whose validating articles were published in Turkish.

We also excluded validated questionnaires that were not intended to primarily assess empathy, but more general related constructs (*e.g.*, social competences and emotion recognition) that only marginally included empathy-related subscales. Specifically, we did not consider in our final qualitative synthesis the following questionnaires: the Emotion Recognition Scale[46]; How I Think Questionnaire measuring cognitive distortions[47]; Interpersonal Gratitude Scale for Children[48]; Infant–Toddler Social and Emotional Assessment with its empathy factor[49]; Children's Behavior Questionnaire with its empathy subscale[50]; Multisource Assessment of Children Social Competence[51]; measure of adolescents' Prosocial Moral Reasoning[52]; Self-Compassion Scale[53]; Toronto Alexithymia Scale[54]; and Impulsiveness and Venturesomeness Scale with its empathy subscale[55]. Most of these measures include an empathy-related subscale or similar factors, which explore either the general construct of empathy or socially oriented behaviors and prosocial skills, without further defining the quality of such phenomenon. As we extensively discussed above, a finer description of empathy-related dimensions is among the main objectives of the questionnaires we selected in the present review, which is far from the scope of the above listed measures primarily intended to assess socioemotional and interpersonal aspects or related constructs.

For historical purposes, we should also mention the Hogan Empathy Scale[56], and the Questionnaire Measure of Emotional Empathy[57]; renowned early measures of empathy that were not used in current research and did not appear in our extensive search.

Study characteristics

Forty-seven primary studies were identified for final analysis, of which 16 were aimed at presenting or validating original questionnaires (Table 1). The sample size ranged from 109 to 2612, and the age range of participants included children and adolescents from 1 to 18 years; participants' gender varied from 46.3% to 100% male. Most study samples included healthy subjects recruited from communities, households, schools, centers and hospitals, except for one study performed only on antisocial convicts recruited from rehabilitation services, and two studies conducted also on patients, recruited from clinical centers, with conduct disorder and ASD, respectively, compared to healthy subjects.

Further characteristics of included studies aimed at validating novel versions or adaptations (n = 6) and translations into different languages (n = 19), or aimed at further evaluating psychometric properties of validated measures (n = 6), are shown in Table 2. Included studies were conducted in European, American and Asian countries, with translations into 11 languages (Basque, Bengali, Chinese, Dutch, French, Italian,

Table 1 Characteristics of included studies aimed at presenting or validating original questionnaires (*n* = 16)

Ref.	Measure	Country	Language	Setting	Participants	Sample size	Age, yr	Gender
Bryant[98], 1984	BEI	NA	English	NA	Healthy	128 + 163 + 73	7/10/14	NA
Litvack-Miller *et al*[99], 1997	IRI	Canada	English	Schools	Healthy	478	7-12	NA
Rey[63], 2003	SME	Colombia	Spanish	Schools (centers)	Healthy + CD	224 + 94	11-18	100/100
Garton *et al*[89], 2005	F&T	Australia	English	Schools	Healthy	413	8-10	53
Jolliffe and Farrington[6], 2006	BES	United Kingdom	English	Schools	Healthy	720	14.8 ± 0.48	50.8
Dadds *et al* [100], 2007	GEM	Australia	English	Schools	Healthy	2612	4-16	52.8
Funk *et al*[82], 2008	CEAQ	United States	English	Schools	Healthy	213	10-13	49.6
Sallquist *et al* [62], 2009	DPES	United States	English	Maternity hospital	Healthy	168	4.49 ± 0.07	52.9
Auyeung *et al* [64], 2009	EQ-C	United Kingdom	English	Schools (centers)	Healthy + ASD	1256 + 265	4-11	46.3/82.6
Rieffe *et al*[83], 2010	EQ	Netherlands	Dutch	Schools and centers	Healthy	109	1-5	47.7
Whitt and Howard[101], 2013	ES-PPI	United States	English	Rehab services	Antisocial	707	15.5 ± 1.2	87
Lopèz-Pèrez and Fernadèz [102], 2014	TECA	Spain	Spanish	NA	Healthy	670	10-16	NA
Vossen *et al*[88], 2015	AMES	Netherlands	Dutch	Households	Healthy	450	10-15	50
Wang and Wang[87], 2015	EToMS	China	Chinese	Schools	Healthy	189	3-6	50.8
Raine and Chen [29], 2017	CASES	United States	English	Community	Healthy	428	11-12	NA
Richaud *et al* [35], 2017	EQ	Argentina	Spanish	Schools	Healthy	479	9-12	46.3

Age is reported in years, as either mean ± SD or age range according to original available data; gender is reported as percentage of males. AMES: Adolescent Measure of Empathy and Sympathy; ASD: Autism spectrum disorder; BES: Basic Empathy Scale; BEI: Bryant's Empathy Index; CASES: Cognitive, Affective and Somatic Empathy Scales; CD: Conduct disorder; CEAQ: Children's Empathic Attitudes Questionnaire; DPES: Dispositional Positive Empathy Scale; EQ-C: Empathy Quotient for Children; EQ: Empathy Questionnaire; ES-PPI: Empathy Scale-Psychopathic Personality Inventory; EtoMS: Empathy and Theory of Mind Scale; F&T: Feeling and Thinking Scale; GEM: Griffith Empathy Measure; IRI: Interpersonal Reactivity Index; SME: Scale to Measure Empathy; TECA: Cognitive and Affective Empathy Scale (Test de Empatia Cognitiva y Afectiva); NA: not available.

Korean, Portuguese, Slovak, Spanish and Turkish). Adaptations included short versions of the original questionnaires and child parent-reported versions of adolescents self-reported measures. Most studies also evaluated the psychometric properties of the measurements, including validity and reliability. The sample size ranged from 51 to 2714.

Measures of empathy

A total of 16 measures were used to assess the construct of empathy in children and adolescents (Table 3). Further details on each measure are provided in Supplementary Materials.

Psychometric properties and validation samples

All measures consisted in Likert scales with number of items and responses varying for each questionnaire, mainly ranging between 12 and 30, with the Dispositional

Table 2 Included studies aimed at validating adaptations (*n* = 6, A) or translations of the included measures (*n* = 19, B), and assessing further psychometric properties (*n* = 6, C)

Ref.	Measure	Language	Sample size
(A) Adaptation studies			
Auyeung *et al*[95], 2012	EQ– adolescent version	English	1243
Bensalah *et al*[60], 2016	BES – child version	French	410
Merino-Soto and Grimaldo-Muchotrigo [103], 2015	BES – short version	Spanish	135
Overgaauw *et al*[59], 2017	EQ – CA version	Dutch	1250
Pechorro *et al*[104], 2018	BES – short version	Portuguese	543
Salas-Wright *et al*[105], 2013	BES – short version	Spanish	208
Sánchez-Pérez *et al*[58], 2014	BES – parent report	Spanish	364
(B) Translation studies			
Albiero *et al*[106], 2009	BES	Italian	665
Albiero *et al*[107], 2010	BES	Italian	1191
Čavojová *et al*[108], 2012	BES	Slovak	429
D'Ambrosio *et al*[109], 2009	BES	French	446
de Wied *et al*[110], 2007	BEI	Dutch	1978
del Barrio *et al*[111], 2004	BEI	Spanish	832
Geng *et al*[112], 2012	BES	Chinese	1524
Soroa *et al*[113], 201	TECA	Basque	504
Grazzani *et al*[114], 2017	EQ	Italian	304
Hawk *et al*[115], 2013	IRI	Dutch	501
Herrera-López *et al*[116], 201	BES	Spanish	747
Liu *et al*[117], 2018	CASES	Chinese	860
Lucas-Molina *et al*[118], 2018	EQ	Spanish	103
Pechorro *et al*[119], 2015	BES	Portuguese	221
Mestre-Escriva *et al*[120], 2004	IRI	Spanish	1285
Rudra *et al*[121], 2016	EQ-C	Bengali	51
Vilte *et al*[122], 2016	CEAQ	Spanish	297
You *et al*[123], 2018	BES	Korean	1524
Zengin *et al*[124], 2018	AMES	Turkish	212
(C) Psychometric Properties			
Anastácio *et al*[125], 2016	BES	Portuguese	1029
Carrasco Ortiz *et al*[126], 2011	IRI	Spanish	721
Holgado Tello *et al*[127], 2013	IRI	Spanish	721
Lasa Aristu *et al*[128], 2008	BEI	Spanish	2714
Lucas-Molina *et al*[129], 2016	BEI	Spanish	2050
Pechorro *et al*[72], 201	BES	Portuguese	377

AMES: Adolescent Measure of Empathy and Sympathy; BES: Basic Empathy Scale; BEI: Bryant's Empathy Index; CA: children and adolescents; CASES: Cognitive, Affective and Somatic Empathy Scales; CEAQ: Children's Empathic Attitudes Questionnaire; EQ: Empathy Questionnaire; EQ-C: Empathy Quotient for Children; IRI: Interpersonal Reactivity Index; TECA: Cognitive and Affective Empathy Scale (Test de Empatia Cognitiva y Afectiva).

Positive Empathy Scale (DPES) and the Empathy Scale derived from the Psychopathic Personality Inventory (ES-PPI) presenting a relatively low number of items,

Table 3 First validation of selected questionnaires (*n* = 16)

Name	Validation	Subscales	*n*	Response	Age	R	IC	Reliability	Criterion	Convergent /divergent
BEI	Bryant[98], 1984	None	22	1 (low) to 5 (high)	C, A	SR	α = 0.54 to 0.79	T-R: r = 0.74 to .83	NA	NA
IRI	Litvack-Miller *et al*[99], 1997	Fantasy; Perspective-taking; Empathic concern; Personal distress	28	0 (not well) to 4 (very well)	C	SR	NA	NA	NA	NA
SME	Rey[63], 2003	None	15	1 (never) to 4 (always)	A	SR	α = 0.78	NA	HC > CD: *P* = 0.008	NA
F&T	Garton *et al* [89], 2005	Affective; Cognitive	12	1 (not like me) to 5 (very like me)	C	SR	α = 0.54 to 0.69	NA	F > M	NA
BES	Jolliffe and Farrington[6], 2006	Affective; Cognitive	20	1 (agree) to 5 (disagree)	A	SR	α = 0.79 to 0.85	NA	F > M: *P* < 0.0001	IRI: r = 0.43 to 0.53; TAS: r = –0.20 to –0.17; SDS: r = –0.11 to 0.00
GEM	Dadds *et al* [100], 2007	Cognitive; Affective	23	–4 (disagree) to +4 (agree)	C, A	PR	α = 0.81 (tot); α = 0.62 to 0.83	IRR: r = 0.40 to 0.38; T-R: r = 0.69	F > M: *P* < 0.001	IQ: r = 0.30 (cogn); CAI-C: r = –0.12 to –0.31; CAI-N: r = 0.05 to 0.25; IRT: r = 0.30 to 0.56
CEAQ	Funk *et al*[82], 2008	None	16	No/Maybe/Yes	C	SR	α = 0.77	RPR = 0.75; RPSI = 1.75	F > M: *P* < 0.01	BEI: r = 0.57; SDQ-PS: r = 0.39; SDQ-CP: r = –0.17; CSDTC: r = 0.39
DPES	Sallquist *et al* [62], 2009	None	7	1 (really untrue) to 4 (really true)	P	PR	α = 0.81	NA	NA	ITSEA-E: r = 0.43; ITSEA-SC: r = 0.35; Task = 0.47
EQ-C	Auyeung *et al* [64], 2009	None	27	1 (disagree) to 4 (agree)	P, C, A	PR	α = 0.93	T-R: r = 0.86	HC-F > HC-M > ASD; *P* < 0.001	SQ-C: r = –0.13
EQ	Rieffe *et al* [83], 2010	Emotion contagion; Attention to others; Prosocial actions	20	1 (never) to 3 (often)	I, P	PR	α = 0.58 to 0.80	NA	NA	NA
ES-PPI	Whitt and Howard[101], 2013	None	5	1 (false) to 4 (true)	A	SR	α = 0.69	NA	NA	BSI-PS: r = 0.11 to 0.30; APSD: r = –0.18 to –0.08; MAYSI-2: r = 0.08 to 0.21
TECA	Lopèz-Pèrez	Perspective	30	1 (disagree) to 4	C, A	SR		NA	NA	NA

	and Fernadèz [102], 2014	taking; Emotion understanding; Personal distress; Empathic joy		(agree)						
AMES	Vossen *et al* [88], 2015	Affective; Cognitive; Sympathy	12	1 (never) to 5 (always)	C, A	SR	α = 0.75 to 0.86	T-R: r = 0.56 to 0.69	F > M; $P < 0.01$	IRI-EC: r = 0.29 to 0.63; IRI-PT: r = 0.21 to 0.45; PBS: r = 0.14 to 0.50; PA: r = –0.07 to -0.36
EToMS	Wang and Wang[87], 2015	Empathy; Nice ToM; Nasty ToM	16	1 (never) to 5 (always)	P	PR	α = 0.71 to 0.83	NA	F > M	WL-NiceToM: r = 0.21; SL-NastyToM: r = 0.33; FB: r = 0.27 (E) –0.28 (NiceToM)
CASES	Raine and Chen[29], 2017	Affective; Cognitive; Somatic	30	0 (rarely) to 2 (often)	C	SR	α = 0.63 to 0.91	NA	F > M	IQ: r > 0; RPAQ-R: r = –0.11; CBCL-Ext: r < 0; APSD: r = –0.12 to –0.39
EQ	Richaud *et al* [35], 2017	Emotion contagion; Self-other awareness; Perspective taking; Emotional regulation; Empathic action	15	1 (never) to 4 (always)	C	SR	ω = 0.70 to 0.76	NA	NA	PBS-C: r = 0.23 to 0.79; PBS-L: r = 0.21 to 0.49; IRI-PT: r = 0.32 to 0.37; PVAS: r = –0.18 to –0.31; EIS: r = –0.24

Validation refers to the original article in which the questionnaire was first validated. Construct refers to the original article in which the definition of the empathy construct for each questionnaire was provided; *n* refers to number of items. Response refers to the number of available Likert-scale responses for each item of the questionnaires. Age refers to the age range in which the original validation of the questionnaire was performed (*i.e.* infants, aged 1–3 years; preschool children aged 3–6 years; children aged 6–13 years; adolescents aged 13–18 years). R refers to type of report, either self- or parent-report. IC refers to internal consistency, measured by either Cronbach's alpha or McDonald's omega. Criterion and convergent/divergent refer to criterion and convergent/divergent validity, respectively. α: Cronbach's alpha; A: adolescents; AMES: Adolescent Measure of Empathy and Sympathy; APSD: Antisocial Personality Screening Device; ASD: autism spectrum disorder; BES: Basic Empathy Scale; BEI: Bryant's Empathy Index; BSI: Brief Symptom Inventory; C: children; CAI: Cruelty to Animals Inventory; CASES: Cognitive, Affective and Somatic Empathy Scales; CBCL: Child Behaviour Checklist; CD: conduct disorder; CEAQ: Children's Empathic Attitudes Questionnaire; CSDTC: Crandall Social Desirability Test for Children; DPES: Dispositional Positive Empathy Scale; EIS: Emotional Instability Scale; EmQue: Empathy Questionnaire; EQ: Empathy Questionnaire; EQ-C: Empathy Quotient for Children; ES-PPI: Empathy Scale-Psychopathic Personality Inventory; EToMS: Empathy and Theory of Mind Scale; F: females; FB: false belief; F&T: Feeling and Thinking Scale; GEM: Griffith Empathy Measure; HC: healthy controls; I: infants; IC: internal consistency; IQ: intelligence quotient; IRI: Interpersonal Reactivity Index; IRR: inter-rater reliability; IRT: Interpersonal Response Task; ITSEA: Infant-Toddler Social and Emotional Assessment; M: males; MAYSI: Massachusetts Youth Screening Instrument; NA: not available; P: preschool children; PA: physical aggression; PBS: Prosocial Behaviour Scale; PR: parent-report; PVAS: Physical and Verbal Aggression Scale; R: report; RPAQ: Reactive–Proactive Aggression Questionnaire; RPR: Rasch Person Reliability; RPSI: Rasch Person Separation Index; SDQ: Strengths and Difficulties Questionnaire; SDS: Social Desirability Scale; SL: strategic lie; SME: Scale to Measure Empathy; SQ-C: Systemising Quotient for Children; SR: self-report; TAS: Toronto Alexithymia Scale; TECA: Cognitive and Affective Empathy Scale (Test de Empatia Cognitiva y Afectiva); ToM: Theory of mind; T-R: Test-retest; WL: White lie; ω: McDonald's omega.

respectively including seven and five items. Reliability assessments (mainly using Cronbach's α) were available for most measures. Original validations of the measures showed questionable to excellent levels of internal consistency, with α values ranging from about 0.54 to 0.93. The lowest levels were found for the F&T and the Bryant's Empathy Index (BEI) questionnaires, while the Empathy Quotient for Children (EQ-C)

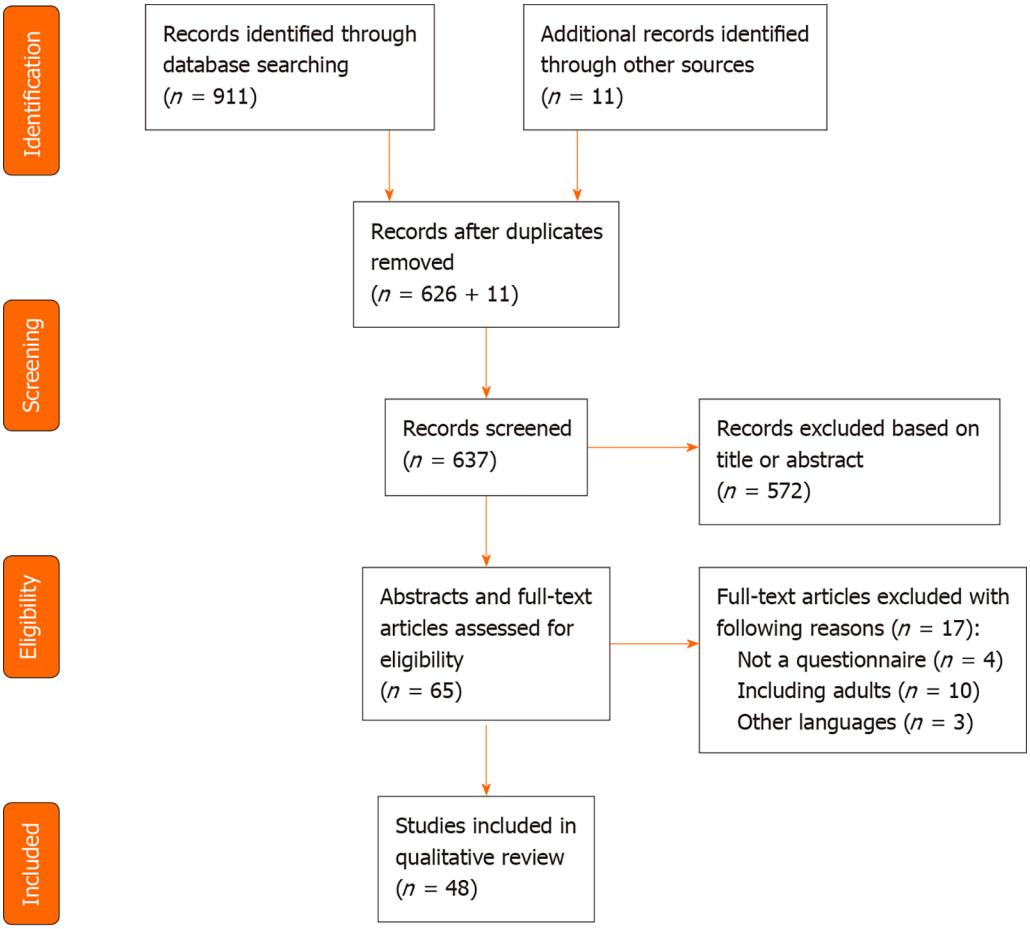


Figure 1 PRISMA flowchart. The process of identification and selection of papers according to PRISMA guidelines is shown in the flowchart. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

demonstrated the highest internal consistency. Test–retest and other reliability measures were uncommon. Good test–retest indexes were found for the BEI and EQ-C scales, while lower levels of reliability were identified for the GEM, Children's Empathic Attitudes Questionnaire (CEAQ) and Adolescents' Measure of Empathy and Sympathy (AMES). Several types of validity assessments were also available. Questionably, criterion validity was mainly based on the finding of higher empathic skills in women than in men. Additionally, the Scale to Measure Empathy (SME) was tested on patients with CD, who showed higher scores than healthy controls, whereas, in the EQ-C, typical individual scored the highest, followed by ASD children who scored the lowest. Convergent and divergent validity was tested by means of several measures, which can hardly allow direct comparisons of the validated questionnaires. Finally, it should be emphasized that, for the ES-PPI scale, content validity appeared questionable; indeed, all its five items could be easily interpreted as related to separation anxiety and interpersonal sensitivity.

As for the type of report, five measures were based on a parental report, while the other 11 were self-reported. Nonetheless, the BES questionnaire, originally developed as a self-report measure for adolescents[6], was also adapted in a parent-report form [58]. The Empathy and theory of mind scale (EToMS), EQ and DPES scales were specifically validated in infants and preschool children, while the SME, BES and ES-PPI measures were originally targeted to adolescents, although the EQ was also adapted for school-aged children and adolescents[59] and the BES for children[60]. No *a priori* restriction was applied to exclude teacher-reported questionnaires; however, no such measure was identified through our search. It is worthwhile noting that the GEM was also previously used for teacher report[61], as well as the abovementioned Infant-Toddler Social and Emotional Assessment questionnaire[62].

Noteworthy, the SME and the EQ-C were originally validated in clinical population of adolescents with CD[63] and children with ASD[64], respectively. In addition, the BEI and the IRI, two of the most widely used scales for empathy, already found a clinical application in the assessment of empathic skills in autism[65,66], conduct

disorders[12] and psychopathic traits[67-69]. Similarly, the GEM has already been used to examine empathy deficits in children with ASD[65], externalizing symptoms with aggressive behavior[61,70], and callous–unemotional traits[71], while the BES has been used in delinquents and institutionalized youths with conduct disorders[72-74]. Those latter three questionnaires also profit from many translations in several languages.

DISCUSSION

Constructs and dimensions: bipartite models

Six measures were monodimensional, while the other 10 appeared to be multidimensional, with variable internal factors. The commonest structure consisted in the combination of the two main components of empathy, namely the affective and cognitive subdivisions, which appear in the F&T, BES and GEM questionnaires. Indeed, most researchers agree on the multidimensionality of the construct of empathy which includes (at least) two main dissociable components[75]. Affective empathy refers to the response to the emotional displays of others, *e.g.*, their facial and vocal expressions and body movements, or to the verbal expression of stimuli with emotional valence[76]. It allows one to automatically relate to other people's emotional states, which is essential for the regulation of social interactions, coordinated activity, and cooperation toward shared goals[24]. Cognitive empathy, instead, refers to the capacity to comprehend another person's emotions, thus leading to the representation of the internal emotional experience of the other[24,76]. Based on the bipartite model of empathy, it has been hypothesized[5,77,78] that a deficit in a specific component relate to a specific neurobehavioral disorder; particularly, cognitive empathy would be specifically affected in ASD, while the affective domain would pertain conduct disorders, especially with callous–unemotional traits, and aggressive behaviors. In his fundamental paper, Blair[5] advocates that "fine cuts" between cognitive and emotional empathy are needed for a better understanding of amygdala dysfunction in psychopathy and autism. More speculatively, Smith[78] identified four main empathy disorders in abnormal developmental circumstances, predicting the existence of two empathy imbalance disorders and two general empathy disorders. The formers include the cognitive empathy deficit disorder (CEDD), consisting of low cognitive ability but high affective sensitivity, and the emotional empathy deficit disorder (EEDD), consisting of low affective sensitivity but high cognitive ability. The latter includes the general empathy deficit disorder (GEDD), consisting of low ability and low affective sensitivity, and the general empathy surfeit disorder (GESD), consisting of high cognitive ability and high affective sensitivity. Specifically, CEDD and EEDD respectively reflect the empathic profiles of autism and psychopathy, while GEDD and GESD that of schizoid personality and Williams syndrome. However, a meta-analysis [79] that confirmed the relationship between empathy deficits and criminal offending found a stronger effect for cognitive empathy deficits than for affective empathy. On the contrary, a review of affective empathy deficits in aggressive adolescents underlined the importance of this latter component of empathy[80]. Questionnaires, such as F&T, BES and GEM, that differentiate between these two components of empathy, could be best applied to the clinical assessment of such conditions in order to confirm or confute those hypotheses.

Hoffman's developmental model-based measures

Among bipartite measures, GEM was largely based on developmental stages of empathic skills proposed by Hoffman[75]. Similarly, both EQ and CEAQ were based on Hoffman's developmental model. While the former actually derives its three subscales from Hoffman's first stages of empathic responses development (*i.e.*, Emotion Contagion, Attention to Others' Feelings, Prosocial Actions), the latter has been validated according to the Rasch model and could thus be considered a unidimensional measure, where subjects and items are placed on the same metric scale: children can be, thus, placed along an "empathy development ruler" to quantify their likelihood of achieving different milestones.

Given its impact on empathy measures, Hoffman's developmental model merits further discussion. According to Hoffman[75], during development empathic responses progressively emerge to reach their final expression in adolescence. He distinguished four levels of empathy, which are believed to develop sequentially[20], although they are not mutually exclusive and, according to de Waal[24], follow one each other to build onto the former levels. the first level is labeled as global empathy or

emotion contagion and manifests itself as early as age 18–72 h and throughout the first year. At this level, newborns attend to others' emotions, although nonadaptively, since witnessing someone in distress may result in a similar affective response[81]. In other words, the theory assumes that humans are congenitally hardwired to automatically imitate and synchronize affective expressions, but infants cannot yet differentiate between self and other, which causes them to act as though what happened to the other person happened to them[20]. Furthermore, infants still have difficulties to control their level of arousal, and the ability for self-regulation is negatively associated with symptoms of emotion contagion[82]. The second level, that can be labeled as attention to others' feelings[83], starts after 1 year of age, and persists during the second year of life. At this level, self-other differentiation, perspective-taking, and emotional regulation gradually develop, and infants become aware that although they feel distressed, it is not oneself but someone else who is in actual danger or pain. Other people's emotions can be thus observed with less personal distress[82]. At the third level, by 2 years of age, concern for others may lead the child to react prosocially (prosocial actions)[83]. During the third year of life, children develop this capacity to intervene on behalf of others; this may take a variety of forms, including helping, sharing, and comforting. Later on, children acquire further social competences, that are frequently used as indicators of the development of a theory of mind (ToM), and progressively develop more effective helping strategies[20]. The fourth level in Hoffman's theory, that is empathy for another's life condition'[83], develops during late childhood. It refers to empathic responses, which are not only confined to the situation, but also with another's general level of distress or deprivation. This empathic level may motivate the child and adolescent to feel empathy for people who live in more unfavorable circumstances, and eventually support them by prosocial behaviors (*i.e.*, donating money to charity funds)[82].

Building on Hoffman's model, Decety and Jackson[25] developed a multidimensional model of empathy in children, on which EQ has been based. In particular, the attention to others' feelings stage proposed by Hoffman[20] is further split in the three components of self-awareness, perspective taking and emotion regulation. Self-awareness requires the child to simultaneously reflect on his feelings and suspend his own experience to evoke the thoughts and feelings of others. This skill is a prerequisite for perspective taking which requires the other to be perceived as different from oneself and yet to be put in one's place. Emotional regulation finally implies the ability for cognitive reappraisal of emotional stimuli in order to change one's own affect. Five subscales of EQ have been built accordingly, namely emotion contagion, self-awareness, perspective taking, emotional regulation and empathic action.

Constructs and dimensions: other multidimensional measures

More recent instruments address new facets of empathy, such as the somatic component, or related constructs, such as sympathy, which might integrate further complexity to the original bipartite model and provide new insights in the understanding of psychological faults in the aforementioned disorders. In particular, the AMES includes a sympathy subscale. While previous empathy scales equate affective empathy with sympathy (*e.g.*, IRI), this validated measure was purposefully intended to distinguish between empathy and sympathy. In this scale, the constructs of affective empathy, cognitive empathy and sympathy were respectively based on the definitions proposed by Mehrabian and Epstein[57] (experience of another person's emotion), Hogan[56] (understanding of another person's emotion) and Clark[84] (feeling concern or sorrow for another person's distress). Thus, affective empathy and sympathy are both conceived as emotional reactions to the perceived emotions of another person; however, in the case of empathy, the emotion is the same as the emotion of the other person (emotion congruence), whereas with sympathy, individuals experience feelings of concern and sorrow about distressful events in another person's life. A third dissociable component, somatic or motor empathy, as defined by Blair[76], can be identified using the Cognitive, Affective and Somatic Empathy Scale (CASES). According to Blair[76], somatic empathy occurs when the individual mirrors the motor responses of an observed actor, as described in the perception–action model of empathy[23]. Somatic empathy is thus conceptualized as more automatic than both affective and cognitive components and consists of a primitive form based on mirror neuron system. In other words, the perception of another person experiencing a specific emotion will elicit a motor act or a somatic body response[29]. Notably, the CASES has been recently applied to capture the multifaceted nature of empathy in the different forms of aggression[85]. In addition, affective, cognitive and somatic empathy could be further distinguished into positive and negative forms, based on CASES subscales[29]. As opposed to negative empathy,

positive empathy represents the expression of happiness or joy that results from comprehending another person's positive emotional state or condition. While CASES subscales could be subdivided in positive and negative components of empathy, Cognitive and Affective Empathy Scale (Test de Empatia Cognitiva y Afectiva; TECA) provide a specific subscale for Empathic Joy and DPES was primarily intended to assess positive empathy in children.

Finally, two facets of ToM, *i.e.*, nice and nasty ToM, are considered in the EToMS. ToM refers to the ability to represent the mental states of others[86]. Whether this concept overlaps with that of the cognitive empathy is still under debate. Indeed, both are perspective-taking capacities that are essential in maintaining a functional social relationship. ToM appears to concern the understanding of epistemic mental states such as knowledge and belief, as well as motivational mental states such as desire and emotion, and their consequences on people's behavior, thus possibly including in itself the concept of cognitive empathy[86]. Alternatively, ToM might be limited to the understanding of the intentionality implied by propositional attitudes, while empathy is linked to emotional connectedness and physiological arousal[87]. The distinction between these nice and nasty components captures the essence of the diverse nature of the social consequences of ToM depending on temperament and social goals. Nice ToM behaviors include cooperating, comforting, and considering feelings of others, while Nasty ToM behaviors include teasing, lying, cheating, and blaming.

Research and clinical applications

Given non-negligible differences in structure and validity between previously described instruments, the selection of questionnaires for research and clinical applications should be tailored to specific needs, depending on setting, goals and characteristics of the studied population.

Older scales, such as the BEI, IRI and BES, benefit from a longer tradition and a wider diffusion with respect to more recent instruments and are preferable in clinical settings. Importantly, the BEI and the IRI are self-report questionnaires validated in English for both children and adolescents and in Spanish for adolescents, while the BES has been validated in several European languages, but also in Chinese and Korean. It is noteworthy that the IRI has been used as reference measure for concurrent validity of four other questionnaires[35,83,88], including the BES[6]. In addition, the F&T has been developed as a modified version of the IRI[89]. Both the IRI and BES have been used in ADHD patients, with or without comorbid conditions such as ASD or disruptive behavior disorders[90]. In this context, they showed significant associations with executive functioning[90]. Interestingly, the IRI has also been used to unravel cognitive empathy deficits in adolescents with anorexia[17]. Several other associations between empathy and psychopathological dimensions, including psychopathy, conduct problems and internalizing symptoms such as anxiety and depression, have been revealed using BES in large samples of adolescent inpatients[91-93]. Finally, the BEI has been found to differentiate between children with conduct disorders and controls[68] and has been associated with conduct problems in children and adolescents with ADHD[13].

Despite their advantages, all these measures are self-reported, which may represent a major limitation when patients with ASD or disruptive behavior disorders are assessed. The GEM could represent a valuable option in this respect. Indeed, the GEM has been developed from the BEI as a parent-report scale for both children and adolescents. For instance, the GEM proved useful in differentiating adolescents with and without ASD, whose BEI scores did not differ[65], and children with and without disruptive behavior disorders based on teacher reports[94]. Importantly, the GEM significantly predicted proactive aggression after 1 year in a prospective study of 6- and 7-year-old children[61]. Another useful parent-report instrument, freely available in several languages, is the EQ-C, that has been validated in preschool children, children and adolescents with and without ASD[64,95]. Discrepancies between parent- and self-reports of empathy have been observed in ASD adolescents using this measure: patients were found to report more empathic features than their parents attributed to them[96]. Further to its focus on autistic traits, EQ-C has also been associated with peer-rated aggression in children[97]. More studies using EQ-C in non-ASD samples are, thus, justified.

Several among the other scales warrant further investigations. Some of the more recently developed instruments, for example, have the advantage to explore newer conceptualizations of interest in research settings. The AMES include a subscale dedicated to sympathy construct, while somatic empathy measurement could be specifically addressed only by CASES. Interestingly, the EQ strictly follows the developmental staging model proposed by Hoffman[20], while the CEAQ has been

validated according to the Rasch model and constitute a "developmental ruler" based on Hoffman's stages. Finally, the EQ, who is also based on Hoffman, is the only available instrument validated in infants, preschool children, children and adolescents.

CONCLUSION

Different measures of empathy have been developed and validated in children and adolescents. Even though construct definitions only partially overlap, affective and cognitive domains are commonly evaluated through separate subscales. Many of these instruments constitute extremely useful clinical tools for evaluating impairments in empathic competences and social skills within neurodevelopmental disorders and psychiatric conditions. However, the choice of the measure to use should clearly vary, depending on the setting and the object of study, and the combination of different assessment methods is recommended in order to foresee further improvements in this field and try to overcome the problem of limited convergence of rating scales with more objective measures. Finally, factor-analytic studies exploring the structure of empathy based on different questionnaires, combined with each other, are warranted, especially in the developmental age, in order to test different conceptualizations of empathy, and to unravel significant non-overlapping facets of the construct.

ARTICLE HIGHLIGHTS

Research background

Empathy deficits significantly contribute to developmental psychopathology. Questionnaires are the most used tools for the assessment of empathy both in adults and in children and adolescents.

Research motivation

No comprehensive overview of validated questionnaires for measuring empathy was available for clinicians and researchers in the neurodevelopmental field.

Research objectives

We aimed to identify and describe empirically validated questionnaires assessing empathy in children and adolescents and to provide a summary of related theoretical perspectives on empathy definitional issues.

Research methods

A systematic review of the literature was conducted according to PRISMA guidelines.

Research results

We identified and described 16 measures used to assess empathy in children and adolescents. Most measures were multidimensional. Several instruments were based on a bipartite model of empathy, with dissociable affective and cognitive components. Other tools were built on Hoffman's developmental model or included new facets, such as sympathy or somatic empathy.

Research conclusions

Different scales are suitable in varying research and clinical settings, depending on the object of study, the clinical population, the age range and the models of interest. The combination of different assessment methods is recommended.

Research perspectives

Future studies shall focus on directly comparing psychometric properties and factor-structure of different empathy questionnaires in multiple clinical and community samples.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 October 19; 11(10): 897-914

DOI: 10.5498/wjp.v11.i10.897

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Neurofeedback for insomnia: Current state of research

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Author contributions: Lambert-Beaudet F wrote the paper and performed the literature search; Journault WG and Provençal AR collected the data; Bastien CH reviewed the paper.

Conflict-of-interest statement: Ms. Lambert-Beaudet reports personal fees from Neuroperforma, outside the submitted work. The other authors declare having no conflict of interests for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Chronic insomnia affects about 6%-13% of the Canadian population. Although treatments already exist, they each have their own issues. Neurofeedback is a neuromodulation technique that specifically targets abnormal brain activity and is gaining attention as a possible insomnia treatment.

AIM

To review the latest studies pertaining to the use of neurofeedback in the treatment of insomnia.

METHODS

In this non-systematic review, only experimental studies assessing the effects of neurofeedback on patients with insomnia were targeted across four bibliographic databases.

RESULTS

A total of 12 studies were retained. All neurofeedback studies included in this study showed a clear improvement of subjective sleep. However, data concerning objective improvement are contradictory. Most studies regarding surface and z-score neurofeedback show that neurofeedback targeting the sensorimotor rhythm in the sensorimotor cortex may help improve subjective sleep. A placebo effect seems also to be present in some studies. Several limitations were present in each study.

CONCLUSION

While studies concerning neurofeedback as a treatment for insomnia are encouraging, many methodological barriers remain to be resolved to prove its efficacy unequivocally. More studies using robust design parameters, as well as the replication of existing studies, are necessary to support neurofeedback as an effective treatment for insomnia.

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Manuscript source: Invited manuscript

Specialty type: Psychology

Country/Territory of origin: Canada

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 27, 2021
Peer-review started: February 27, 2021
First decision: May 5, 2021
Revised: May 18, 2021
Accepted: August 27, 2021
Article in press: August 27, 2021
Published online: October 19, 2021

P-Reviewer: Vyshka G
S-Editor: Ma YJ
L-Editor: A
P-Editor: Guo X

Key Words: Sleep; Insomnia; Hyperarousal; Biofeedback; Neurofeedback; Neurotherapy

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Core Tip: Insomnia is a sleep disorder that is extremely prevalent in the general population. The current treatments offered tend to ignore the neurological marker of insomnia. Neurofeedback is a type of neurotherapy that is based on training one's electrical brain activity to treat multiple ailments including insomnia. In this review, we discuss the different studies that have been published in the last few years concerning the use of neurofeedback to treat insomnia and what needs to be improved in this domain of research.

Citation: Lambert-Beaudet F, Journault WG, Rudziavic Provençal A, Bastien CH. Neurofeedback for insomnia: Current state of research. *World J Psychiatr* 2021; 11(10): 897-914
URL: https://www.wjgnet.com/2220-3206/full/v11/i10/897.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i10.897

INTRODUCTION

Insomnia

Sleep difficulties are very common, with an estimated one-third of adults around the world being dissatisfied with their sleep[1]. Furthermore, approximately 6%-13% of the general population meets all criteria necessary for the diagnosis of insomnia disorder[1-4]. Insomnia is a sleep disorder characterized by a dissatisfaction with the quantity and/or quality of sleep[5]. This dissatisfaction must be associated with difficulty falling asleep, maintaining sleep and/or waking up early in the morning. These difficulties must be present at least 3 nights a week for the past 3 mo and must cause distress or impaired functioning[5].

Not only does insomnia causes distress, it is linked to multiple psychopathologies. In fact, there is a 40% co-occurrence between insomnia symptoms and mental illness [6]. Insomnia is also linked to multiple health problems, such respiratory and cardiac diseases[7]. Insomnia affects everyone differently, and the profile of individuals that suffer from it is very heterogeneous[8]. However, it is widely recognized that hyperarousal plays an important role in insomnia[9-12]. For example, insomnia is linked to an increased heart rate[13], increased facial muscle tension[14] and a higher rate of cortical activation[15]. According to Bonnet and Arand[16], insomnia is a hyperarousal disorder and its treatment should aim to decrease arousal.

Currently, there are two main types of treatment: Medication or cognitive behavioural therapy for insomnia (CBT-I)[17]. Medication has been shown as effective for treating insomnia, while its effects are mainly short-term[18]. Unfortunately, long-term use of medication causes undesirable side effects, such as cognitive and motor coordination problems, physical dependence and rebound insomnia[18,19].

Several studies support the effectiveness of CBT-I in reducing insomnia symptoms, such as wakefulness after sleep onset (WASO) and sleep efficiency (SE)[17,20,21]. However, there is a lack of research establishing that CBT-I leads to significant changes in sleep onset latency (SOL)[22]. It is also important to note that only 60% of individuals receiving CBT-I are considered good sleepers after treatment[23]. The literature showing that CBT-I is effective at decreasing hyperarousal is also quite scarce. In that regard, Altena *et al*[24] have shown a frontal hypoactivation after CBT-I, while Cervena *et al*[25] have shown an increase in slow waves and a slight decrease in beta activity after CBT-I.

While medication is recommended only as a short-term treatment for insomnia with non-equivocally lacking effectiveness in the long-term for treating insomnia[18], CBT-I focuses mainly on behaviors and cognition surrounding sleep[26]. Because hyperarousal has been identified as a predisposing and maintaining factor in insomnia disorder[27,28], it would be advisable to offer treatment, such as neurofeedback (NF), that aims to modulate hyperarousal and which could offer long-term benefits.

NF

NF is a sub-category of biofeedback, a technique where one learns to modulate bodily functions, such as heart rate, through feedback[29]. To do this, biofeedback uses various stimuli corresponding to one's physiological characteristics and presents them to the client (feedback). The client then uses this information to modify his/her physiological functioning[30]. In the case of NF, the physiological signals used and modulated are brainwaves.

NF is based on the principle of operative conditioning[31]. There are many different types of NF, but they all have in common the use of visual and/or auditory stimuli (video, music, *etc*.) as positive reinforcement presented when electroencephalographic (EEG) activity corresponds to the training goal. The withdrawal or modification of this stimulus is used as a negative punishment to inform the individual that his/her brain functioning is diverging from the training goal. With this basic principle, NF can both encourage and dissuade certain brainwaves[32].

The history of neurofeedback is strongly intertwined with that of sensorimotor rhythm, beginning with the studies of Sterman *et al*[33]. Their 1967's study, a precursor in neurofeedback research, led to the discovery of the sensorimotor rhythm (SMR), a brain state present only during periods of motor stillness. The aim of these studies was to reproduce the internal inhibition observed in Pavlov's previous studies, when presenting contradictory conditioned responses. Pavlov had observed that the modification of conditioned responses caused, in time, lethargy and even sleep in dogs. When they attempted to reproduce this effect with cats, they noticed that the suppression of a conditioned response, and thus of movement, was linked to a bursting rhythm localized at the sensorimotor cortex. This rhythm was thus named SMR (11-15 Hz)[34]. They reported that this EEG pattern strongly resembled the sleep spindles observed during sleep. In these studies, they also found that cats were able to induce this rhythm voluntarily. These cats then showed an increase in the density of sleep spindles as well as a reduction in sleep stage transitions and thus prolonged sleep[35].

Since then, research on neurofeedback as a treatment for sleep difficulties often focuses on the control of SMR. The frequencies associated with SMR vary between studies but they usually are around 12 to 15 Hz, sometimes including higher or lower frequencies. Some studies uses the inhibition of higher frequencies, such as high beta frequencies (20-35 Hz), to reduce alertness, whereas others enhance slower frequencies, from delta (less than 4 Hz) to alpha frequencies (8-12 Hz), to promote deep relaxation[36].

The various NF techniques can be divided into two broad categories: closed-loop NF and open-loop NF[37,38]. Open-loop NF aims at regulating EEG activity by using auditory and visual stimuli not representative of the EEG activity at that time. Rather, this type of NF aims at synchronizing brain activity to rhythmic external stimulus. Closed-loop NF, on the other hand, is based on real-time EEG activity to determine characteristics of the transmitted feedback (positive reinforcement or negative punishment)[39]. NF is not regulated by any governmental body. However, some organizations such as the Biofeedback Certification Institute of America and the International Society for Neurofeedback and Research offer guidelines for biofeedback training as well as certifications for clinicians. The list of NF techniques presented in the Results section is not exhaustive and refers only to those used by the studies included in this review.

MATERIALS AND METHODS

This review uses a non-systematic approach to give a general idea of the literature available in the field of NF. Articles were collected on four bibliographic databases: Psycnet, PubMed, Cochrane Central Register of Controlled Trials and Web of Science. For the bibliographic searches, the term "neurofeedback" was combined with the term "insomnia" for all categories with the "AND" operator. Synonyms and Medical Subject Headings for each term were combined with the "OR" operator.

Once articles were identified, those dealing directly with the use of NF for the treatment of insomnia were extracted. Studies focusing on insomnia treatment as a comorbid disorder were included, while those papers simply mentioning sleep difficulties, without any emphasis on it, were excluded. Only scientific articles and abstracts from experimental studies were used for this study. Case studies and retrospective studies were excluded. We included all sleep-related measures and outcomes. Results pertaining to other disorders are not discussed in this review since

our aim is to focus on the efficacy of NF as an insomnia treatment.

Overall, 12 articles were included in this study, including 6 on surface neurofeedback (NFS), 2 on z-score NF, 2 on open-loop NF, 1 on high-resolution, relational, resonance-based, electroencephalic mirroring (HIREEM) NF and 1 on Brain Music NF (see Figure 1 for the schematic of the bibliographical search).

RESULTS

NFS

NFS is a type of closed-loop NF that uses only two to four electrodes and targets a reduced number of cortical regions as well as a reduced number of brainwaves[40]. During NFS, the client will be presented with his/her own EEG activity, at a specific region, in the form of visual and/or auditory stimuli. The purpose of NFS is to increase/decrease specific frequencies at specific locations. Our review identified six studies using NF for the treatment of insomnia (see Table 1 for the study parameters and Table 2 for a summary of the results).

This study[41] used a counterbalance within-subject design with placebo to demonstrate whether NF can improve sleep and cognitive performance in individuals with insomnia. A single group of 24 participants with primary insomnia received 10 sessions of NF during which they had to increase the power of their SMR (12-15 Hz) at C3. They also received five placebo neurofeedback (PF) sessions where they trained the amplitude of non-SMR frequencies at random.

They found a significant increase in SMR power at C3 after NF sessions, with a non-significant increase at C4. No significant change was observed in SMR power across the PF sessions. They reported an increase in fast sleep spindles during non-rapid eye movement (referred to as NREM) but no change in slow sleep spindles. Sleep spindles are EEG waves of a frequency of 12 Hz (slow sleep spindles) to 14 Hz (fast sleep spindles) that are typical of NREM sleep, especially stage 2 sleep[42]. They are markers of the wake-sleep transition and have been theorized to play a role in learning and plasticity as well as in sleep protection by inhibiting sensory processing[43]. Slower sleep spindles have been found in sleep-maintenance insomnia and are linked to insufficient sleep pressure and thus difficulties maintaining sleep[44]. Accordingly, they observed a decrease in the number of awakenings and an increased duration of stage 3 following the NF sessions. The researchers also reported a decrease in subjective sleep complaints following NF and PF sessions, but it was not possible to determine whether this decrease was solely due to NF. On the other hand, physical quality of life improved regardless of the treatment offered, suggesting a placebo effect.

In conclusion, they found that it is possible for individuals with insomnia to increase SMR power, which allowed an objective modification of certain aspects of sleep architecture (N3, fast sleep spindles, number of awakenings). Thus, SMR NF in the sensorimotor cortex would improve sleep architecture, subjective sleep quality and physical quality of life. It is important to note that there is a strong chance that a placebo played a role in this study.

Schabus *et al*[45] tried to replicate their 2014 findings in a double-blind, placebo-controlled study. To do so, they used four groups: a primary insomnia group (INS: n = 16), an insomnia misperception group (MP: n = 9), a sleep control group (n = 26) and a NF control group (n = 12). The MP group was composed of individuals that met the subjective criteria for insomnia but not the objective criteria. The control groups were composed of healthy individuals. The INS and MP groups received 12 NF sessions (increase SMR) and 12 PF sessions (increase non-SMR frequencies at random) in reverse order. Polysomnographic (PSG) data were recorded before and after each condition (NF and PF) for the INS and MP group as well as an initial PSG for the sleep control group. The NF control group received only 12 NF sessions.

They found that participants had a higher SMR power after NF sessions than after PF sessions, suggesting the ability to self-regulate SMR frequencies. The MP group had higher SMR power following the NF sessions than the INS group. The NF control group also had an increase in SMR power, but that increase stabilized after one NF session. The MP group required four sessions and the INS group required six to achieve stabilization of the increase of SMR power. Contradictory to their 2014 study, no significant changes were found in sleep architecture following NF or PF sessions. The authors found that participants' subjective complaints were reduced following the NF as well as the PF sessions, regardless of group (INS/MP), with a larger decrease for participants who started with the NF sessions.

Table 1 Study parameters for surface neurofeedback

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Control/sham condition
Schabus *et al*[45]	16 primary insomnia; 9 insomnia misperception; 26 sleep control; 12 NF control (criteria: PSG, PSQI, DSM-IV)	Insomnia group: 38.59 ± 11.18-year-old (range: 27- to 50-year-old) / 19 females and 6 males; Sleep control: 35.52 ± 10.63 (range: 24- to 47-year-old) / 19 females and 7 males; NF control: 26.67 ± 4.46 (range: 22- to 32-year-old) / 6 females and 6 males	C3	Enhance: SMR (12-15 Hz)	12 sessions NF 12 Sham (mixed); (2-4 sessions/wk); 8 5 min blocks/session	Enhance random frequencies (other than SMR rhythm) during present sessions (½ first; ½ second)
Schabus *et al*[41]	24 primary insomnia (criteria: PSQI, SIS-D)	34.83 ± 10.6 (range: 24- to 46-year-old) / 17 females and 7 males	C3	Enhance: SMR (12-15 Hz)	N/A	Enhance random frequencies (other than SMR rhythm) during preset sessions
Cortoos *et al*[46]	9 tele-NF; 8 tele-biofeedback; 12 controls	Tele-NF: 41.5-year-old / 3 females and 6 males; Tele-biofeedback: 43.8-year-old / 3 females and 5 males; Controls: 44.4-year-old/5 females and 7 males	Cz	Enhance: SMR (12-15 Hz); Inhibit: Theta (4-8 Hz) and high beta (20-30 Hz); Biofeedback: 50 Hz	18 sessions of 1 h (2-3 sessions/wk)	Control group
Arns *et al*[49]	51 ADHD (SMR: 27, TBR: 10, SMR + TBR: 14); 28 controls	ADHD: (range: 6- to 53-year-old) / 14 females and 37 males; Controls: (range: 21- to 64-year-old) / 15 females and 13 males	SMR: C3;Cz or C4; TBR: Fz; FCz or Cz	Enhance: SMR (12-15 Hz); TBR (20-25 Hz and 15-20 Hz)	29-31 sessions (2-3 sessions/wk); 8 5 min blocks/session	Control group
Sungwon[51]	14 participants; NF; CBT-I (criteria: ISI)	N/A	N/A	Inhibit: Beta	N/A	CBT-I
Shin[50]	4 mild insomnia (Registered at a sleep clinic)	34.8 ± 5.3-year-old/1 female and 3 males	N/A	Enhance: Theta and sigma; Inhibit: Beta	N/A	None

ADHD: Attention deficit hyperactivity disorder; CBT-I: Cognitive behavioral treatment for insomnia; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth edition; NF: Neurofeedback; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; SIS-D: Structured clinical interview for sleep disorders; SMR: Sensorimotor rhythm; TBR: Theta/Beta ratio.

The researchers therefore suggested that INS and MP participants were able to regulate SMR frequencies following the NF sessions and that this may lead to a decrease in the subjective symptoms of insomnia. However, the subjective effects reported by this study appear quite similar to those obtained with the placebo effect and were not associated with objective changes in PSG data.

In this 2010 study, Cortoos *et al*[46] investigated whether NF can reduce symptoms of primary insomnia using a pretest post-test design with control group. The study consisted of 17 participants with insomnia randomly distributed in two groups for: receipt of 18 NF sessions (n = 9) or receipt of 18 biofeedback sessions (BF; n = 8). A third group of 12 good sleepers was used as a control group to compare initial PSG data. PSG data were recorded for all participants at the beginning of the study and then at the end of the NF/BF sessions for the NF and BF groups.

The NF and BF sessions were ran at home and participants were responsible for electrodes' placement. The BF sessions consisted of relaxing the forehead muscles using information from an electromyogram. The NF group had to increase SMR (12-15 Hz) amplitude and reduce the amplitude of theta (4-8 Hz) and high beta (20-30 Hz) frequencies at Cz.

PSG data from both groups (BF; NF) showed a significant decrease in SOL and WASO. The BF group had a greater decrease in SOL (44.9%) than the NF group (39.7%), while the NF group showed a greater decrease in WASO (53.6%) than the BF group (13.2%). Both groups also had increased rapid eye movement (referred to as REM) duration. Only the NF group reported a significant increase in total sleep time (TST). The sleep diaries of the NF group also reported a significant decrease in SOL and WASO, and an increase in TST. The BF group only reported significant improvement in SE in their sleep diaries.

Cortoos *et al*[46] therefore concluded that NF allows for more significant sleep improvements, particularly TST, than biofeedback. Results of the BF group had a caveat since no participant reported abnormal forehead muscle tension or high somatic arousal compared to the control group, which can indicate that somatic

Table 2 Summary of the results on surface neurofeedback

Ref.	Sleep outcomes measurements	Results
Schabus *et al* [45]	Objective: PSG; EEG; Subjective: PSQI; WHOQLA; SSS	Significant effect for NF compared to PF: (1) Higher SMR-power directly after each session[b]; and (2) Higher spindle density for the fast spindle type (C3 only)[b]; Significant effect for NF and PF: (1) Reduction of subjective sleep complaints after 12 sessions[b]; and (2) Unspecific increase of physical quality of life[b]; Significant effect for INS compared to MP: (1) More wake time[b]; and (2) Less stage 2, stage 3 and REM[b]; Significant effect for MP compared to INS: Higher SMR-power after each session[b]
Schabus *et al* [41]	Subjective: PSQI, Sleep Diary, WHOQLA, WMS-R, BSI	Significant effect only for NF: (1) Increase of SMR activity at C3[a]; (2) Decrease of the number of awakenings[a]; and (3) Increase of stage 3[a]; Significant effect for NF and PF: (1) Reduction in subjective sleep complaints[b]; and (2) Increased physical quality of life[b]
Cortoos *et al* [46]	Objective: PSG; Subjective: Sleep diary	Significant effect only for NF: (1) Decrease of SOL[a] and WASO[a] (Sleep diaries)[a]; and (2) Increased TST[a] and SE[a] (Sleep diaries); Significant effect only for BF: Increase of SE[a] (Sleep diaries); Significant effect for NF and PF: (1) Decrease of SOL[a] and WASO[a] (PSG); and (2) Increase of REM sleep;
Arns *et al*[49]	Subjective: PSQI	Significant effect only for SMR: (1) Decrease of SOL[d]; (2) Decrease of SOL (40.1 min to 19.1 min)[b]; and (3) Correlation between the change in inattention and changes in PSQI[b] and SOL[b]; Significant effect for SMR + TBR: Decrease of SOL (25.8 min to 18.8 min)[a]
Sungwon[51]	Objective: EEG (resting state); Subjective: ISI, PSQI, DBAS	Significant effect only for NF: (1) Decrease of ISI[b]; (2) Changes in PSQI[a]; and (3) Decreased Beta power; Significant effect only for CBT-I: (1) Decrease of ISI[a]; (2) Changes in PSQI[a]; and (3) Decrease of DBAS[a]
Shin[50]	Objective: EEG	Significant effect only for NF: Decreased spectral power for theta[a]

[a]$P < 0.05$.
[b]$P < 0.01$, pre *vs* post.
[d]$P < 0.01$ pre-treatment *vs* mid-treatment.
BF: Biofeedback; BSI: Brief Symptom Inventory; DBAS: Dysfunctional Beliefs and Attitude about Sleep; EEG: Electroencephalography; INS: Primary insomnia; MP: Insomnia misperception; NF: Neurofeedback; PF: Placebo neurofeedback; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; REM: Rapid eye movement; TBR: Theta/Beta ratio; SE: Sleep efficiency; SOL: Sleep onset latency; SMR: Sensorimotor rhythm; SSS: Stanford Sleepiness Scale; WASO: Wakefulness after sleep onset; WHOQLA: World Health Organization Quality of Life Assessment; WMS-R: Wechsler Memory Scale – Revised.

arousal was not an issue for the participants. It is also important to note that although sleep diaries in the NF group showed an overall improvement in sleep, there was no significant change in sleep diaries completed the day after the PSG recordings compared to those completed at home. This suggests a strong influence of the environment on the results, which is in accordance with sleep studies that have shown the effects of sleep laboratories on sleep parameters[47,48].

The purpose of this study[49] was to verify the presence of sleep difficulties in individuals with attention deficit disorder (ADHD) and to test the effects of SMR and theta/beta (TBR) NF on ADHD symptoms and the associated sleep difficulties. This study used an open-label design including a control group (n = 28) and an ADHD group (n = 51). The ADHD group was divided into three groups: a group (SMR) receiving NF sessions aimed at increasing SMR (n = 27), a group (TBR) aimed at increasing beta waves outside SMR frequencies (20-25 Hz, 15-20 Hz) and inhibiting theta waves (n = 10), and a last group receiving NF sessions combining SMR and TBR treatments (n = 9). The remaining five participants of the ADHD group were used as a control group for the initial measures. On average, participants received 30 NF sessions.

SMR and TBR NF significantly decreased SOL (SMR: 40-19 min; TBR: 26-19 min). SMR NF resulted in a rapid decrease in SOL between pre-treatment and mid-treatment measurements, followed by a plateau until the end of the sessions. TBR NF showed opposite results, *i.e.* a non-significant decrease for the first half of treatment and then a strong significant decrease during the second half. Strangely, they found that individuals who learned to increase their SMR during SMR NF sessions reported a smaller decrease in their Pittsburgh Sleep Quality Index (PSQI) score.

In this study[50], the researcher wished to quantify the effects of NF on the brain waves of individuals suffering from insomnia. To do so, he administered a randomized series of NF (increasing theta and sigma waves and decreasing beta waves) and placebo (PF) sessions.

By comparing the NF sessions to the PF sessions, Shin found a significant decrease in theta spectral power in the NF group. Mental slowness (delta to alpha ratio) increased slightly, but not significantly, during NF sessions. This study therefore suggests that individuals experience greater fatigue during NF sessions, which could

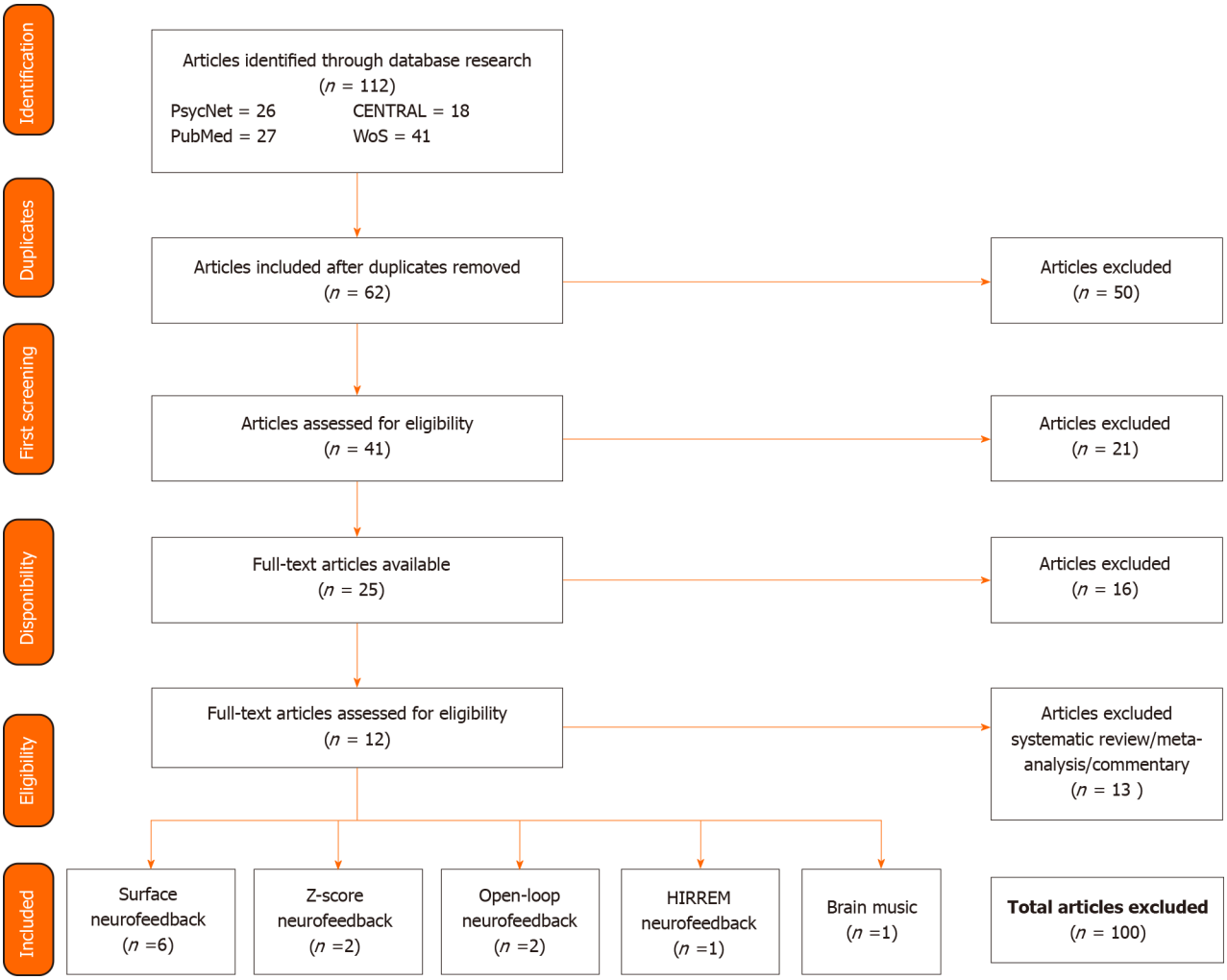


Figure 1 Summary of the bibliographical research. A total of 112 articles were extracted from four different databases. Fifty articles were excluded at first since they were duplicates. Twenty-one articles were excluded as they were not focused on neurofeedback as a treatment for insomnia. Sixteen articles were excluded since they were not available to study. Thirteen articles were then excluded as they were not experimental studies. A total of 100 articles were excluded. Twelve articles were included in this review. HIRREM: High-resolution, relational, resonance-based, electroencephalic mirroring; WoS: Web of Science.

explain sleep improvements by increasing sleep pressure and thus facilitating sleep onset.

In this abstract, Sungwon[51] verified whether NF is as effective as CBT-I in treating insomnia. A total of 14 participants were randomly assigned to two groups, one receiving NF sessions and one receiving CBT-I sessions. An EEG (resting state) was recorded before and after each condition.

Participants in both groups reported significantly lower Insomnia Severity Index (ISI) and PSQI scores following treatment. In contrast, only the CBT-I group reported a significant decrease of their Dysfunctional Belief and Attitudes about Sleep scores and only the NF group showed a significant decrease in beta potency. The author therefore concluded that both treatments are effective in reducing insomnia but each in its own way. NF reduces hyperarousal, while CBT-I reduces dysfunctional thoughts about sleep.

The majority of the studies aimed at increasing SMR in the sensorimotor cortex[41,45,46,49], and the number of sessions varied between 12 to 31 sessions at a minimum of two sessions per week. A total of four studies concerning NFS used a combination of objective and subjective measures[41,45,46,50]. All studies except one used subjective measures[50]. All of the studies using subjective measures reported a subjective improvement of sleep, such as SOL[46,49], WASO[41,46], TST[46] and subjective sleep complaints[41,45]. The results of objective measures were varied, but the recurrent finding was that EEG activity was changed after NF sessions, which suggests that the participants were capable of modulating their own EEG activity[41,45,50]. These results support the idea that modulation of EEG activity is possible and that it can reduce insomnia symptoms. However, a placebo effect was noted in the

Schabus[41,45]'s studies.

Z-score NF

Z-score NF (live z-score based training, LZT) is also part of the closed-loop NF family and is based on the same principles as NFS. The main difference is that the LZT is not based on the power spectral analysis of specific brain waves but on its comparison to the population average. To do this, EEG activity is compared in real time to a normative database that accounts for age, gender and handedness to provide a score (Z-score) representing the position of the client related to the population average[40, 52]. The purpose of LZT is to bring this score closer to the population average (Z = 0). This type of NF therefore aims to normalize brain activity at one or multiple cerebral regions. We included two studies in our literature review (see Tables 3 and 4).

The purpose of this study[53] was to determine whether two z-score NF protocols, one SMR protocol and one QEEG-guided and individualized protocol, can lead to a decrease in sleep and daytime dysfunction associated with insomnia. This pilot study used a randomized, parallel-group, single-blind experimental design.

All participants received a maximum of 15 sessions. They could stop sessions early when they felt that their insomnia had been successfully treated or when they were able to achieve normalization (Z-score < 0.5) of 80% of the trained variables for 80% of the training time. The SMR group had to increase, at Cz and C4, SMR frequencies (12-15 Hz) while inhibiting theta (4-8 Hz) and high beta (25-30 Hz) waves. Participants in this group also had to ensure that amplitudes and brain connectivity at the trained regions remained closed to the database average. Participants in the individualized protocol group were given a protocol tailored to their own brain activity, based on the four brain regions with the highest level of abnormal activity (highest z-score) identified during a quantitative EEG (QEEG). QEEG is the quantification of EEG data in order to compare it to databases or to highlight specific waveform components[54]. During training, the individualized protocol group had to normalize z-scores that deviated from the average of the database of delta, theta, alpha and beta waves amplitudes present in the four regions with the highest Z-score. They also had to normalize coherence, asymmetry and lag phase.

By the end of sessions, all participants had achieved the normalization of 80% of the trained variables for 80% of the training time. On average, participants achieved normalization of 88% of the variables for 80% of the training time (range: 80%-95%). On the other hand, no participant achieved complete normalization of all trained variables. Approximately 50% of participants were able to train closer to normal in their last session, with a Z-score of ± 1.5 on all variables. All but one participant of the SMR group managed to increase their SMR Z-score at Cz and C4, but there was no overall significant increase in SMR. For participants in the individualized protocol group, the proportion of abnormal z-scores was significantly lower after treatment for all brain regions, particularly for delta and beta waves. There was no significant difference between the different regions due to the individual aspect of their training protocols.

Following training, all participants reported an ISI score below the insomnia threshold (< 10) and 7 of the 8 participants reported a PSQI score below the insomnia threshold (< 5). The eighth participant had a PSQI score of 6. Half of the participants reported a decrease in WASO. Seven of the eight participants also reported an increase in TST. Six participants completed the 6-9 mo follow-up for the ISI. Five of the six participants remained below the threshold for insomnia, with three experiencing further sleep improvements in the following months. The sixth participant reported the same score as at their initial ISI.

In conclusion, the researchers reported that the SMR protocol achieved the same results as the individualized protocol in a simpler manner. They suggested that z-score NF is effective in the treatment of insomnia and that effects may last, or even improve, in the months following the end of treatment.

Information for this study[55] is taken from a brief abstract. The aim of this study was to observe the neurometric changes generated by 20 Z-score NF sessions. To do so, authors compared the initial and final QEEGs of 6 patients from the Nepsa clinic. A significant difference in the z-scores was found between the initial and final QEEGs, *i.e.* Z-scores out of range of the -1 to 1 average. Participants were also more likely to decrease the Z-score (normalization) than to increase it. Authors also reported a subjective improvement in patients' symptoms, who were asked to rate them on a visual scale. No information was given on the specific symptoms improved. Researchers therefore suggested that z-score NF allows normalization of EEG activity and the alleviation of insomnia symptoms.

Table 3 Study parameters for z-score neurofeedback

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Sham condition
Hammer *et al*[53]	5 SMR; 3 IND	49.63-year-old / 5 females and 3 males	SMR: Cz and C4; IND: 4-channel (highest abnormal sites)	SMR: Increase SMR (12-15 Hz) and inhibit excessive theta (4-8 Hz) and high beta (25-30 Hz). Normalization at Cz/C4 (Amplitude, connectivity); IND: Normalization of amplitudes, coherence, asymmetry and phase lag with the highest Z-scores (> 1.96) at the 4-channels trained	Range: 9 to 15 sessions; (2 sessions/wk); 20 min/session	None
Perez-Elvira *et al* [55]	6 participants with insomnia and/or learning disorder	Range: 16- to 30-year-old	N/A	Normalization of the highest Z-score	20 sessions; (2 sessions/wk)	None

IND: Individualized protocols; SMR: Sensorimotor rhythm.

Table 4 Summary of the results on z-score neurofeedback

Ref.	Sleep outcomes measurements	Results
Hammer *et al*[53]	Objective: QEEG (Z-score); Subjective: PSQI, ISI	Significant effect only for SMR: Decrease z-score; Significant effect only for IND: Decreased proportion of abnormal z-scores at all 19 sites[b], especially for delta[b] and beta[b] bands; Significant effect for SMR and IND: (1) Decreased score for ISI[b], for PSQI[b]: All participants finished under the threshold for insomnia (ISI < 10; PSQI < 5, except 1 at 6); and (2) Increased TST[b]; Results of the 6-9 mo follow up: 5 out of 6 participants remained below the ISI threshold for insomnia; 3 of the 5 improved during the months following the end of the treatment
Perez-Elvira *et al* [55]	Objective: QEEG; Subjective: Visual analogue scale on their symptoms	Significant effect: (1) Significant difference of 5.70% between pre- and post-QEEGs; (2) More probable to normalize then to get further away from normalization[a]; and (3) Improvement of symptoms

[a]$P < 0.05$.

[b]$P < 0.01$ pre *vs* post.

IND: Individualized protocol; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; QEEG: Quantitative Electroencephalogram; SE: Sleep efficiency; SMR: Sensorimotor rhythm; TST: Total sleep time.

Only two studies on Z-score NF were included in this review. Both of them found that participants were able to normalize their EEG activity in the NF sessions by reducing the proportion of abnormal z-scores. The number of sessions varied between nine and twenty sessions, at a rate of two per week. They all found a subjective improvement in sleep following the treatment. Only one study described the subjective improvement and the authors reported an increase of TST[53]. None of the studies used a placebo group. Both studies supported the idea that normalization of EEG activity was possible through z-score NF.

High-resolution, relational, resonance-based, electroencephalic mirroring

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) NF is a closed-loop NF technique aiming at improving neurodynamic self-regulation by presenting the brain with its own oscillatory pattern through auditory stimuli[56]. To do this, EEG activity is recorded at two locations (usually contralateral) on the scalp [57]. This activity is then translated into music based on the dominant frequency of the client's EEG activity. This creates a resonance between the music and the neural oscillations, thus encouraging self-regulation. A HIRREM session consists of several training protocols[56]. HIRREM NF thus aims at regulating the general oscillatory pattern. Only one study using this technique was used in this review (see Tables 5 and 6).

In their 2012 study, Tegeler *et al*[56] investigated whether HIRREM reduces insomnia symptoms. To do so, they used a randomized, unblinded, wait-list control, crossover, superiority study design. A first group (n = 10) received eight to twelve HIRREM sessions plus usual care, while a second group (n = 10) was placed on a wait-list control (usual care).

The researchers reported a significant drop of 10.3 points in ISI scores for participants following the HIRREM sessions, with 9 out of 10 participants in the HIRREM group now being just below the threshold (15 to 21) for moderate insomnia.

Table 5 Study parameters for high-resolution, relational, resonance-based, electroencephalic mirroring neurofeedback

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Sham condition
Tegeler *et al*[56]	10 HUC; 9 UC (criteria: Clinical diagnosis (clinician referral and ISI)	HUC: 41.3 ± 17.5-year-old / 8 females and 2 males; UC: 49.5 ± 8.1-year-old / 6 females and 4 males	Two-channel, changes with each protocol	Each session comprises of 4-8 protocols	8-12 sessions of up to 90 min over 3 wk	None

HUC: HIRREM plus usual care; ISI: Insomnia Severity Index; UC: Usual care (wait-list).

Table 6 Summary of the results on high-resolution, relational, resonance-based, electroencephalic mirroring neurofeedback

Ref.	Sleep outcomes measurements	Results
Tegeler *et al* [56]	Subjective: ISI	Significant effects only for HUC: Decrease of ISI score[b]; Significant effect only for UC: Decrease of ISI score, once the treatment is received

[b]$P < 0.01$ pre *vs* post.

HUC: HIRREM plus usual care; ISI: Insomnia Severity Index; UC: Usual care (wait-list).

The wait-list group also reported a significant decrease in ISI scores, but only 6 out of 10 participants scored below the threshold for moderate insomnia (< 15) after receiving HIRREM sessions. ISI scores were stable for both groups 1 mo after the last HIRREM session. Finally, they appeared to have decreased in high-frequency brainwaves power (23-36 Hz) in temporal regions (T3/T4). A power decrease in high frequency brainwaves (23-36 Hz) in temporal regions (T3/T4) was also observed for all participants. However, no information was provided as to whether this decrease was statistically significant.

Open-loop audio-visual entrainment

Open-loop audiovisual training (AVE) is, as the name suggests, part of the open-loop NF category. It is designed to stimulate the cerebral cortex using goggles and headphones programmed to provide visual and auditory stimuli in the form of synchronous lights and auditory pulsations. Stimuli are constant, repetitive and delivered at a predetermined frequency to arouse the thalamus and the neo-cortex, where visual and auditory information will be respectively processed[38]. This stimulation is believed to synchronize neuronal activity between the thalamus and neo-cortex, which will subsequently spread to the rest of the cerebral cortex *via* thalamo-cortical-thalamic circuits[37,38]. A total of two articles using this technique were included in this review (see Tables 7 and 8).

In their study, Tang *et al*[37] used a pretest and post-test design to test the effectiveness of a daily 30-min AVE at bedtime for 1 mo in a group of 8 elderly people with chronic insomnia. Participants were required to use an AVE device. Sound stimuli gradually decreased from 8 Hz (theta/alpha), associated with a mental state of relaxed wakefulness, to 1 Hz (delta), which is usually associated with deeper sleep.

At the end of the month, researchers observed that 63% of participants no longer met the threshold for insomnia according to scores on the ISI (ISI ≤ 7). Although there was no significant pre/post difference in the overall ISI score, authors reported a significant improvement for daytime functioning and sleep quality. Clinical parameters reported in sleep diaries (SOL, TST, WASO) were not significantly different between subjects when compared across the five measurement periods (pre-treatment and subsequent 4 wkly sessions). However, the trend between weeks suggested that AVE effects appeared right in the first week and then stabilized.

As a follow-up to their 2015 study, Tang *et al*[58] recruited 19 seniors to test AVE NF on EEG activity during a 30-min session. To do so, they randomly assigned participants to two groups, AVE NF ($n = 9$) or placebo stimulation ($n = 7$). The placebo stimulation session consisted of a color changing dim light provided by goggles and a monotonous tone decreasing in frequency from 1 Hz to 0.2 Hz. The AVE group received flashing light (red and green spectrum) from goggles as well as auditory pulsations gradually changing from 10 Hz (alpha) to 2 Hz (delta). A QEEG (5 min, eyes closed, resting state) was recorded before and during both AVE and placebo

Table 7 Study parameters for open-loop audiovisual training neurofeedback

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Sham condition
Tang *et al* [37]	8 chronic insomnia (criteria: ISI)	88 ± 8.7-year-old / 7 females and 1 male	N/A	Progressive reduction from 8 Hz to 1 Hz with flickering lights	30 sessions of 30 min (at bedtime) over 4 wk	None
Tang *et al* [58]	9 insomnia and chronic pain AVE; 7 insomnia and chronic pain Placebo (criteria: ISI)	AVE group: 67.2 ± 5.0-year-old / N/A; Placebo group: 69.6 ± 4.4-year-old / N/A	N/A	Progressive reduction from 10 Hz to 2 Hz with pulsing lights	1 session	Progressive reduction from 1 to 0.2 Hz with constant dim light changing in color

AVE: Open-loop audiovisual training; ISI: Insomnia Severity Index.

Table 8 Summary of the results for open-loop audiovisual training neurofeedback

Ref.	Sleep outcomes measurements	Results
Tang *et al* [37]	Subjective: ISI, PSQI, sleep diary	Significant effect: Decreased ISI score (15.6 ± 4.8 to 8.0 ± 6.4)[b]
Tang *et al* [58]	Objective: QEEG; Subjective: ISI, PSQI	Significant effect only for AVE: Increased delta frequencies' absolute power on all 19 EEG channels; Significant difference between AVE and placebo: Delta power at Cz

[b]$P < 0.01$ pre *vs* post.

ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; QEEG: Quantitative electroencephalogram.

sessions. Results were compared to a normative database taking into account age, gender and handedness.

At initial assessment, all participants had higher absolute power for high-beta (21-34 Hz) and gamma waves (35-45 Hz) than the database. After the experimental session, participants in the AVE group had a significant increase in the absolute power of delta waves on all 19 EEG channels, while participants of the placebo group had no significant EEG power change in any band frequency. Participants of the AVE group had higher delta power at Cz after the AVE sessions than the placebo group. Specific brain regions displaying a significant increase in delta power in the AVE group were central (Cz), fronto-parietal (*i.e.*, Fp) and occipital (*i.e.* O1 and O2) regions. According to the authors, this study showed that AVE NF allows for immediate changes in the EEG activity.

Both studies on AVE neurofeedback were conducted by Tang *et al*[58]'s research team. One study concerned the subjective improvement of sleep after 30 sessions and found that AVE neurofeedback led to a significant decrease of ISI scores. The second study concerned the objective effect of one session of AVE NF on brain activity. They found that participants presented increased delta frequencies, even when compared to a placebo group. This supports the idea that AVE NF can modulate EEG activity and improve insomnia symptoms.

Brain music

Brain Music NF is a type of open-loop NF that closely resembles HIRREM. This type of NF also uses musical compositions generated from one's brain activity. Music is created from various EEG parameters, such as frequency ratios of certain waves modifying octave selection, tempo, volume in the left or right ear, *etc.*[59]. Music tracks are built to correspond to two states of rest, one active and one calm, and to encourage brain functions associated with these mental states[60]. However, unlike HIRREM, the musical compositions are generated during an initial assessment, and the individual under training then listens to their own musical compositions at home, without being connected to an EEG. Thus, although the music reflects a specific brain state experienced by the individual in the past, it does not adapt to the individual's EEG fluctuations during a training session[60]. Very few papers regarding this technique were found, and only one met our inclusion criteria (see Tables 9 and 10).

DuRousseau *et al*[60] investigated whether a music-based NF treatment could improve sleep quality, mood and daytime functioning in policemen and firefighters

Table 9 Study parameters for brain music

Ref.	Groups	Age/sex	Electrode placement	Protocol	Sessions	Sham condition
DuRousseau *et al*[60]	15 OPS support; 20 first responders; 6 controls	Range 24- to 58-year-old / 13 females and 28 males	F3; F4; C3; C4	Brain Music (1-4 Hz up to 30 Hz)	N/A	Enhance random frequencies during preset sessions

OPS: Operational support; N/A: Not available.

Table 10 Summary of the results on brain music neurofeedback

Ref.	Sleep outcomes measurements	Results
DuRousseau *et al*[60]	Subjective: 128-questions homemade questionnaire	Significant effect for all groups (except control): Improved sleep quality[a]

[a]$P = 0.05$ pre *vs* post.

using a pre-test and post-test design with a control group. Participants were then given a copy of their personalized composition and had to listen to it during the day for 4 wk.

The study consisted of three groups: a group of individuals working in operational support of first responders ($n = 15$), a group of first responders ($n = 20$) and a control group of first responders ($n = 6$). Individuals in the control group were given the composition of another participant. Results are based on a 128-item questionnaire created by the group that focuses on mood, sleep quality, insomnia level, job performance and life satisfaction.

They found an improvement in sleep quality in 90% of participants (all groups combined) but more particularly in the two experimental groups. However, since the control group also reported improvements, it is possible that a placebo effect is present or that simply listening to music before falling asleep promotes sleep. Moreover, this study is based only on a subjective measure, the 128-item questionnaire. It is therefore difficult to estimate whether changes are really due to Brain Music training and not to a placebo effect.

A majority of studies included in this review were centered on closed-loop NF, precisely NFS[41,45,46,49-51] and Z-score NF[53,55]. They mostly used a protocol aimed at increasing SMR (12-15 Hz)[41,45,46,49,53].

All 10 studies using subjective measures reported subjective improvements in sleep [37,41,45,46,49,51,53,55,56,60]. The subjective sleep characteristics that most often appeared to be improved by NF, regardless of type, are SOL[46,49], WASO[45,46] and TST[46,53]. Another subjective improvement reported by studies is subjective complaints[41,45]. It should be noted that some studies[37,51,56,60] only reported changes in sleep using general questionnaires' scores (ISI, PSQI, *etc*.), without providing details on the specific sleep characteristics that had improved.

Only six out of twelve studies[41,45,46,50,55,58] used objective measures to verify sleep improvement. The objective results are very varied and do not reach a clear consensus. The PSG data were mostly used to verify sleep characteristics used in subjective measures such as TST, WASO, *etc*. Only a few studies used polysomnography to verify changes to sleep architecture. For example, Schabus *et al*[41] reported an increase in N3, whereas Cortoos *et al*[46] reported an increase of REM. The EEG data were mostly used to assess EEG activity right after the NF sessions. Most studies using objective measures reported a change in the brainwave-trained[41,45,50], supporting the idea that an individual is capable of regulating his/her own EEG activity. However, this change is not always sustained over time[41], which calls into question the idea of learning retention and its application in everyday life.

DISCUSSION

Results extracted from this review show that, although the use of NF seems encouraging for the treatment of insomnia, there are few studies in this field of research. Moreover, available studies often show methodological or clinical limits.

In general, NF appears to lead to improvements in sleep quality for individuals with insomnia, particularly SOL, WASO, TST, SE and subjective sleep complaints. In a few cases, improvements allowed participants to no longer meet the criteria for an insomnia diagnosis[53,56]. Studies on the objective effects of NF report conflicting results, so it is difficult to draw a clear conclusion. Still, most studies agree that objective measures of NF seem to confirm its ability to alter positively the electrical functioning of the brain during training, but it is unclear whether this effect persists in everyday life. It will be necessary for future studies to implement objective measures, such as EEG and PSG, to prove the efficacy of NF.

The most commonly used training protocol is aimed at increasing SMR oscillations in the sensorimotor cortex. The SMR is linked to a state of relaxed wakefulness as well as to NREM sleep[35,41]. The decrease in insomnia symptoms with the increase in SMR frequencies tend to support the hyperarousal model that postulates that individuals with insomnia present higher mental and physiological hyperarousal. For example, compared with good sleepers, individuals with insomnia generally present an increased power in fast EEG frequency bands during sleep[61]. By increasing SMR, NF counteracts for cortical hyperarousal associated with insomnia by attenuating the power of high-frequency EEG waves[41]. Some studies have used neuromodulation techniques, other than NF, that aim at reducing hyperarousal, such as transcranial magnetic stimulation, to treat insomnia, but the evidence remains scarce[62]. It would be interesting to verify the efficacy of NF for the treatment of other disorders that are characterized by hyperarousal such as post-traumatic stress disorder[63]. Such studies would provide additional support to the hypothesis that neuromodulation techniques, such as NF, reduce insomnia symptoms by decreasing cortical hyperarousal.

Common problems in NF studies

Although results of studies included in this review are encouraging for the future of NF in the treatment of insomnia, several impediments are present and obscure its effectiveness.

Lack of consensus and replication: First, there is a lack of consensus on the type of protocols to be used according to the different NF techniques. While trained brainwaves vary greatly between studies, guidelines for duration, frequency and number of sessions are necessary. For example, NF duration ranges from eight to thirty sessions at a rate of two to four sessions per week. However, some researchers suggest that up to 40 sessions of NFS and 10 sessions of LZT NF are necessary to change efficiently behavior and symptoms[64,65]. Therefore, without clear guidelines, it is challenging to replicate each study correctly. It is therefore essential for researchers to share clearly how their study was conducted and to be consistent in terms of training parameters. It is only then that researchers will be able to replicate other studies adequately.

Small sample size: NF studies generally have a small sample size. Whether this is because of the complexity of studies or the burden imposed upon participants during participation, larger sample size would be indicated to obtain reliable results that could then be generalized to the general population or the one under study. There is still undeniable advocacy towards the scientific community to run large-scale NF studies.

Insufficient placebo group: Studies with a pre-/post-test design without a placebo or even a control group are currently the standard in NF research. Studies using placebo groups often report a placebo effect that is sometimes equal to that of the one provided by NF. Reported placebo effects should be considered with caution because it is difficult to create a placebo treatment that can actually mislead participants without mistakenly producing neurophysiological neurological changes. For example, in the Schabus *et al*[41,45] studies, the placebo groups had to increase power in random EEG frequencies, other than those targeted by the experimental condition. Although these EEG frequencies were varied with each session to avoid long-term learning, it is difficult to argue that the placebo treatment was completely inactive. There is always the possibility of learning to modulate random EEG activity[66]. Since no alternative currently exists, the Schabus *et al*[41,45] studies represent the golden standard for placebo protocols. Understandably, to develop a truly inactive placebo treatment will require improvements to the ones currently used in research.

Possible bias: Sadly, only the study by Schabus *et al*[45] used a double-blind design. Although some studies are single-blind, it is difficult to ignore researchers' bias of their studies' outcomes, especially if participants are aware of the training condition. It

would therefore be crucial to use the double-blind design more often.

Limits

This review also has limitations. First, we focused on studies dealing with the treatment of insomnia. Studies using the general term of 'sleep difficulties' were not included and it would be interesting in the future to include these studies since favorable results with the use of NF were obtained. For example, NF was found to help reduce sleep difficulties in individuals that suffered from childhood obesity[67], seizures[68], fibromyalgia[69], stroke[70], traumatic brain injury[71], post-traumatic stress[71], *etc*. Second, our approach was a non-systematic one. It is possible that some studies have been discarded but would have contributed to our understanding of this encouraging treatment for insomnia.

CONCLUSION

Altogether, results of research using NF as a treatment for insomnia are encouraging with respect to subjective improvements in insomnia symptoms, specifically SOL, WASO and TST. The increase in SMR frequencies coupled with a decrease of insomnia symptoms, as seen in multiple studies, seem to support the hyperarousal model of insomnia. It will be interesting to study the efficacy of NF on other disorders characterized by hyperarousal, such as post-traumatic stress disorder, as a way to confirm if this technique reduces sleep difficulties by reducing cortical hyperarousal. However, multiple improvements are necessary in NF research beforehand to create reliable studies.

According to our literature review, there is an urgent need of double-blind controlled or placebo-controlled experimental design with larger sample sizes. Once this becomes usual in NF research, the replication of studies to strengthen NF's status as an alternative to traditional insomnia treatment will be possible.

ARTICLE HIGHLIGHTS

Research background

Insomnia is one of the most common sleep disorder among adults in Canada and the treatments currently available present some limits. Neurofeedback (NF) is a technique that could offer a new way to treat insomnia through the regulation of abnormal brain activity.

Research motivation

In the last few years, NF has been gaining attention in the research community. However, there are only a few studies in the field of insomnia and their methods and results vary greatly. It is important to offer a consensus as to what is missing and what is successful in NF research so that future researchers can build upon what has already been done.

Research objectives

The goal of this review was to summarize the research that has already been done concerning the use of NF in the treatment of insomnia. This summary includes the common results and methodologies used in NF research as well as the improvements that need to be implemented.

Research methods

Data from experimental studies pertaining to the use of NF as a treatment of insomnia was collected from four bibliographical database and analysed. A short summary containing the methods, the results and the conclusions for each study was provided as well as for each NF type. A general summary was presented for all the studies included in this review.

Research results

A total of 12 studies on 5 different types of NF were used in this review, including surface NF, z-score NF, open-loop NF, high-resolution relational resonance-based

electroencephalic mirroring NF and Brain Music NF. All the studies reported a clear improvement of subjective sleep, but there was no consensus concerning objective sleep. Many studies suggest that training the sensorimotor rhythm in the sensorimotor cortex improves subjective sleep. However, many studies also point out a possible placebo effect. The diversity of methods used across studies hinders on the ability to replicate NF studies and create robust studies.

Research conclusions

The findings of this study support the hyperarousal model of insomnia, by increasing sensorimotor rhythm frequencies to decrease insomnia symptoms. To verify this theory, further research should be conducted to study the efficacy of NF to treat other disorders that are characterized by hyperarousal. This review has also point out the limits that currently plague NF research such as small sample sizes, inexistent placebo group and double blind design.

Research perspectives

This review has brought to light the need for more double-blind controlled and placebo-controlled experimental design and bigger sample size to prove the efficacy of NF as a treatment of insomnia.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contribution of Laval University for providing the resources necessary for the bibliographic searches.

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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 November 19; 11(11): 915-1166



Published by Baishideng Publishing Group Inc

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RESPONSIBLE EDITORS FOR THIS ISSUE

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NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
November 19, 2021

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World Journal of Psychiatry

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World J Psychiatr 2021 November 19; 11(11): 915-936

DOI: 10.5498/wjp.v11.i11.915

ISSN 2220-3206 (online)

FIELD OF VISION

How does the 'environment' come to the person? The 'ecology of the person' and addiction

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Author contributions: Tretter F and Loeffler-Stastka H conceived the topic in iterative discussions; Loeffler-Stastka H contributed the question how comes "the social into the mind" and added the psychoanalytic concepts; Tretter F provided expertise for systems theory, concepts on addiction, and the ecology of the person.

Conflict-of-interest statement: The authors declare no conflict of interest regarding our manuscript.

Country/Territory of origin: Austria

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in

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Abstract

Currently, psychiatry lacks a field that can be called "theoretical psychiatry", which uses theoretical concepts and explanatory models: The main stream of research is to collect data of all kinds in the hope that the computational Big Data approach will shed a bright light on the black box of mental disorders. Accordingly, the biology-based Research Domain Criteria of the National Institute of Mental Health have been established. However, as philosophical analyses of concepts and methods have shown, several epistemological gaps stand in the way of a consistent multilevel understanding of mental disorders. Also, the implicit ontological problems in the biological reduction of the psychosocial level and in the integration of so-called hard and soft disciplines are mostly left out. As a consequence, a non-reductive psychological theory of mental disorders is sought that also integrates correlating biological and sociological issues. In this context, one example of promising nonreductive psychiatric research is the option of systems/network psychopathology. The possibilities for integrating different psychological perspectives are highlighted for the field of addiction research and treatment, where pragmatic behaviorist approaches dominate over the theory-based practice of psychoanalysis. In comparing the theoretical constructs of these two approaches, the relevance of the concept of "(social) environment" as the wealth of influential sociocultural factors is discussed at levels superior to the interpersonal micro-level, namely the organizational meso- and societal macro level, which is not sufficiently considered in current biopsychiatry. On this basis of argumentation, the usefulness of grounding and framing psychiatry through the field of ecological sciences, especially human ecology, is demonstrated. Finally, to this end, an outline of an ecological model of mental health and illness is presented.

Key Words: Systems/network psychopathology; Theoretical psychiatry; Ecology of the person; Psychoanalytic object relations theory; Addiction; Mind; Resilience

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Received: May 1, 2021
Peer-review started: May 1, 2021
First decision: June 17, 2021
Revised: June 30, 2021
Accepted: September 2, 2021
Article in press: September 2, 2021
Published online: November 19, 2021

P-Reviewer: Hosak L
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Liu JH

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Core Tip: Similar to theoretical medicine, theoretical psychiatry and its engagement with systems/network psychopathology has a research gap, and so we shed light on the question of how the "social", respectively the environment, manifests itself in the person. Using addiction as an example, we explore systems theoretical and psychoanalytic concepts to provide a framework for understanding the sociocultural, interpersonal, and human ecological factors that impact mental health and illness. This theoretical framework provides a way to understand conceptually and structure computer-collected Big Data. The fact that humans are "situated subjects" implies a broader view of a systemic ecology of the person to guide processes of change in mental health, whether for prevention or treatment.

Citation: Tretter F, Loeffler-Stastka H. How does the 'environment' come to the person? The 'ecology of the person' and addiction. *World J Psychiatr* 2021; 11(11): 915-936
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/915.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.915

INTRODUCTION

Nothing is as practical as a good theory[1].

Theory in psychiatry?

The call for "theoretical psychiatry" is not often made, but it seems a useful, but challenging, task[2,3]. But what is a "theory"?

Even in the philosophy of science there is not much consensus about essential features of theories. Empiricists see theories as final stages of induction, while constructivists see even observations as a kind of theories. Here the hybrid Kantian position might be useful, which distinguishes between empirical and theoretical knowledge but claims that they are related. In this context, and with respect to applications in medicine/psychiatry, there are several descriptions of theories to consider: Theories can be characterized essentially as "because" answers to "why" questions that appeal to causal principles, such as in classical physics: The apple falls from the tree because of gravity, namely, reciprocal forces that are inherent in all objects and are supposed to be exchanged between them[4]. Applied to medicine/psychiatry this could mean: The disease arose because the person was exposed to stressors. Scientific theories are logically consistent statements about reality. Their central concepts must be clearly defined ("disease") and should be supported by empirical data[5]. In this regard, theories are based on a set of empirically verified hypotheses, where hypotheses are mainly statements with an "if x, then y" or "the more x, the more y" structure. Hypotheses are inductions from empirical data and, once strongly confirmed, are called empirical laws and can be developed into a more complex construct (gravity) that requires and allows for further explanation. In medicine (and psychiatry), a hypothesis is very often already classified as a theory. However, hypotheses are not sufficient to understand complex phenomena such as health and disease, because confirmed empirical laws are only a basis of theories, which expand into highly formalized concepts, at least in physics and chemistry. Of course, as derived statements about reality, theories should be falsifiable and therefore must be "grounded" by observations and data, otherwise they are according to Karl Popper only immunized belief systems. Theories intend causal explanations and should thereby also the range of their validity: Isaac Newton's theory of gravity is useful for everyday mechanics, but Albert Einstein's relativistic theory of gravity also covers processes in the subatomic world.

In summary, and consistent with such global descriptions, theories can be understood as explanations, in particular, of new observations and data by "nomological deduction", which also enable predictions, even if these are only probabilistic and not deterministic in character[6]. In short, theories enable the ordering of observations.

Although this metatheoretical conception of a theory has been questioned in philosophy of science, at least with respect to the relevance of principles (or laws) in biology, psychology and sociology (nomological explanations), mechanistic models can be a sufficient formulation of a theory[7]. In this context, the systems theory view, as we partially apply it here, has a paradigmatic epistemological position that refers to principles such as "dynamic equilibrium" and focuses on building testable models of networks and circuits[8-11].

THEORY IN PSYCHIATRY – ONLY A BIOLOGICAL REDUCTION WITHOUT INTEGRATION?

Again, the call for a "theoretical psychiatry" is a challenging task[2,3] due to its complexity. Therefore, further elaboration is needed.

Diversity of psychiatric "theories" – Different perspectives

Within the description of theories and a brief review of the history of the scientific roots of psychiatry at the transition from the 19th to the 20th century, different approaches can be identified[12]: Kraepelin[13] emphasized experimental psychology in order to obtain more accurate data on mentally ill patients[13], while Jaspers[14] focused on the world of experiences with his influential phenomenological psychopathology. Another psychiatric giant of the times, Bleuler[15] had sympathies for the broader framework of psychoanalysis launched by Freud[16] and based on qualitative data and extensive theories[16].

After this period of more or less psychological approaches to mental disorders, the discovery of successful psychopharmaceutical approaches in the 1950s ushered in biological psychiatry, which continues to dominate psychiatric thinking today[17,18]. Also in the 1950s, social psychiatry began the scientific study of the social dimension of mental disorders leading, for example, to the discovery of class-specific inequality in the incidence of mental disorders[19]. However, the study and organization of health care was also increasingly a topic of social psychiatry[20]. In particular, international comparisons of epidemiology and culture-specific conceptions of mental health and health care demonstrated the need for cultural psychiatry[21].

In agreement with these main disciplinary directions of psychiatric research, it must be acknowledged that mental disorders as objects of knowledge in psychiatry are multidimensional phenomena, which - already for their differentiated description - require biological, psychological and sociological concepts and research methods, and which are in principle explained by the integrative bio-psycho-social model proposed by Engel[22] in the late 1970s. This model was intended to allow each individual mental disorder, such as addictions, to be represented within an integrative conceptual framework[23].

However, in the 1980s, and contrary to Engel's suggestion, scientific psychiatry became increasingly one-dimensional through the extensive use of, of course valuable, (neuro) biological methods, data, and perspectives. As a result, sophisticated imaging techniques can be used in clinical research together with molecular biological tools that generate a huge amount of data, and new psychiatric drugs have also been developed. In line with this development, the book "Brave New Brain" in 2001 summarized the value of the biological approach in psychiatry as a strong programmatic perspective that is still growing and even dominating psychiatric thinking[24]. In terms of practical psychiatry, psychological techniques [*e.g.*, cognitive behavioral therapy (CBT)][25] have been explored and added to pharmaceutical treatment. Planning and intervention in family and community relationships also became an important topic in multidimensional practical psychiatry.

Hypotheses were formulated at the theoretical level, derived from biological data and obtained using increasingly sophisticated technical methods. These hypotheses have been empirically tested, but almost no complex theoretical concepts have been developed that are "explanatory" in the strict sense. Mainly statistically based constructs like the "(individual's) susceptibility to stress" were supposed to explain the variance in the data world[26]. However, as mentioned at the onset, such constructs are not theory in the sense of theory in the context of physics.

Criteria for the research domain – an integrative framework?

As a consequence of data, and technology-driven biological psychiatry based on the initial brief description of theory, we are currently confronted with an almost theory-

free psychiatry that wants to refer to data, hopefully Big Data[27]. This-critically speaking-empirical and biocentric complex research program was supposed to be integrated a few years ago by the conceptual framework of Research Domain Criteria (RDoC)[28]. RDoC essentially aims to integrate behavioral science and neuroscience into a matrix of five functional domains, namely social functions, cognitive functions, positive valence functions, negative valence functions, and basic regulatory functions described by different types of data such as genetics, molecules, cells, circuits, physiology, behavior, and even self-reports. This comprehensive approach promises more order in understanding the wealth of knowledge in psychiatry. It ultimately aims at a bioscience-based new taxonomy of diagnoses and thus stands in some contrast to the Diagnostic Statistical Manual[29] with its symptom-centered taxonomy of classical clinical psychiatry as used by clinicians.

One of the most impressive positive examples that fits well with RDoC is the neurobiology of addiction, which was developed before RDoC. Most notably, Koob and Le Moal[30], Koob[31], and Koob and Volkow[32] have stimulated theory development in addiction research through neurobiology[30-32]. For example, they consider the opposing functional organization of the reward system (nucleus accumbens) and the stress/punishment system (amygdala) and outline a stage-based concept that shifts from a brain center-oriented paradigm to a ("systemic") neuro-network view. It also draws on the behavioral biology of addiction but is likely to be of limited use in clinical work. We will add to this approach in the second part of this paper.

In general, RDoC seems to favor "behavioristic psychology" over phenomenological approaches to psychological issues, especially psychopathology. Apparently, there is also a relevant epistemological gap between objective and detached psychiatric research in the laboratory (third person perspective), based on physiology and behavioral science, and subjective and interactive clinical observation and practice at the beside, albeit standardized, based on self-reports (first and second person perspective). Some of these basic epistemological contradictions have already been discussed (*e.g.*, in relation to the interdisciplinary study of working memory[33] and also in relation to the foundations of RDoC)[34].

Epistemological gaps – challenges for bridging concepts

These philosophical (or metatheoretical) issues in psychiatry are rarely discussed and only by a few researchers[35-38]. Regarding the theoretical integration of knowledge, due to the multiplicity of methods that are used to study mind and brain[39,40], there are at least three main gaps that cannot be reduced by physicalism and cannot be captured by a non-reductive physicalism within an "integrative neuroscience", since these multiple dimensions seem to be emergent properties of humans[41,42]: (1) Intradisciplinary integration in biological substrate research: The main problem of contemporary biology is related to the part-whole problem and implies that molecular biological knowledge cannot be easily linked to questions of whole-organism physiology: This problem also implies that data from physics and chemistry are difficult to combine. For example, there is no consistent theory of information processing of the synapse that relates electrical digital phenomena, such as spiking frequency of presynaptic neurons, to proportional transmitter release and analogous changes in membrane potential of the postsynaptic neuron by integrating electro-physiology with molecular biology/pharmacology that can "explain" and justify robust formal theories of macro-physiological processes of the brain such as epileptic seizures[43-45]; (2) Interdisciplinary integration between biology and "psychological sciences" (psychology, psychopathology, psychotherapy, clinical psychiatry, *etc.*): In addition to the gaps in intradisciplinary integration, no "theory" (as described at the beginning) but only mechanistic neurobiological models are developed to explain mental phenomena and their disorders. A simple reduction of the mind to the brain has not yet been realized and is perhaps impossible in principle[46]. As noted neuropsychiatrist Nancy Andreasen has also pointed out[47], "The application of technology without the guidance of astute clinicians with specific expertise in psycho-pathology will be a lonely, sterile and perhaps fruitless endeavor." Consistent with this insight, the foundation of clinical psychiatry remains descriptive psychopathology as the "interdisciplinary, theoretical and an empirical study of subjectivity"[48]. The use of technology in clinical psychiatry has been a major challenge. Accordingly, it is obvious that not only biological research is fruitful, but also a structural-functionalistic psychology without explicit reference to neurobiology can produce new insights: A "network psychopathology" that emphasizes the interactions between symptoms, as realized by Denny Borsboom's group at the University of Amsterdam using graph theoretical tools, offers new possibilities to reconstruct psychopathology without

neurobiology[49]. The results of this approach can be aligned with neurobiology, but there is no must[50]. This view fits well with our systems model of mind proposed later; (3) Interdisciplinary integration between psychiatry and social sciences (*e.g.*, integration of mental/behavioral disorders and sociocultural issues). In other words: How does the sociocultural environment enter the mind/brain? Basically, it must be conceded with Popper[51] that there is an ontological uniqueness of the sociocultural world ("World 3"[51]). His analysis also justifies a more or less substrate-free social and cultural research in psychiatry, which cannot be replaced by the very limited "social neuroscience". The latter seems to be limited to the micro-level of interpersonal interaction. Moreover, the social world is only one dimension of the real environment, because there are natural objects, technical objects, social objects, cultural objects *etc.*, as will be explained in the third section of this paper. In particular, the closures due to coronavirus disease 2019, by deprivation show the influence of the whole environment on mental health. For this reason, we focus on the last point, namely the notion of environment.

To conclude this first chapter, our next step is to highlight some of these theoretical and metatheoretical issues, namely the difference between external and internal conditions of mental health-through challenges to a theory of addiction. We focus on the clinical limitations of the stimulus response model and the need for subjectivity and a differentiated model of the mind that also includes essential elements of the diversity of the factor "environment" in an ecological perspective. One goal is to find a productive theoretical bridge between behavior therapy and psychoanalysis, with an emphasis on the latter, even while being aware of basic criticisms from philosophy of science[52,53].

THEORIES OF ADDICTION – FROM PSYCHOANALYSIS TO THE STIMULUS-RESPONSE MODEL TO PSYCHOANALYSIS AND THE ECOLOGICAL PERSPECTIVE

As mentioned earlier in reference to RDoC, addiction is currently discussed primarily from the perspective of neurobiology. Addiction psychiatry is now a laboratory- and animal-centered perspective and has fewer and fewer connections to the clinical perspective. Addiction research is even conceptually reshaping clinical thinking. Therefore, the question now arises as to how the critical arguments made earlier fit with a "practical theory" of addiction: Are clinical observations more "real" than laboratory data? Since addiction is primarily a psychological problem, it should be kept in mind that the history of concepts in psychology (and psychiatry) shows that the subjective perspective has been increasingly avoided, and "objectification" has become the guiding feature of scientific psychology/psychiatry. Although psychoanalytic explanations of alcohol addiction were among the first theories of addiction, due to various shortcomings in empirical research, concepts, methodology, theory, and the practicality of treating mental disorders through psychoanalysis, the behaviorist perspective prevailed among professionals. However, since addiction is a chronic disease, in rehabilitation and long-term treatment some of the aspects proposed by psychoanalysis, especially in relation to the holistic domain (the person in the world), still seem relevant. If the concept of environment is constructed in a differentiated but integrated way, encompassing both significant people and drugs as components of the person's environment, a human ecological perspective might also be conceptually connectable to psychoanalysis. This will be discussed in the final section. In this section, we will focus on the components of theoretical compatibility of psychoanalysis and cognitive behavioral therapy theory as conceptual building blocks for an integrative model of the mental.

The early psychoanalytic view of addiction – the topic and the structural model

Briefly characterizing some of the roots of psychoanalysis, it is a complex theory of human behavior and a treatment method that emphasizes unconscious repressed affective-motivational drives of behavior. It focuses on the hypothetical functional structure and dynamics of the mind and assumes a powerful unconscious layer of the mind. These are the key points that Sigmund Freud elaborated with the first topic model (conscious/preconscious/unconscious) and the second topic model, the structural model (id, ego, superego). In relation to addiction, Freud[54] around 1898 interpreted addiction as a kind of masturbation as a substitute behavior for (sexual) dissatisfaction[54,55]; it is a purely self-centered behavior necessary to experience

pleasure. Later, in the 1930s, Fenichel[56] interpreted excessive drinking as a merging of the id with the ego, in order to fight together against a rigid but mainly implicit superego, which can additionally cause guilt and shame, even in a circular causal process[56]. With regard to systems theory, this model identifies the central driving force of addiction as an intrapsychic difference between a set of desired values and real values that cannot be changed by the person, which is why he or she experiences a tension that can be subjectively reduced only by consuming psychoactive substances.

Remarkably, the therapeutic effectiveness of psychoanalytic treatment of addicts did not reach widespread use, and soon the behavioral approach in psychotherapy began its triumph. The problem of addicted clients at first contact – even after detoxification - did not show stable sobriety for analytic treatment, the lack of experimental and quantitative empirical evidence, and also the apparent arbitrariness of theoretical concepts devalued psychoanalysis of addiction and hindered the development of psychoanalysis in this clinical field. As a basic result, a fundamental reorientation toward learning theory occurred in clinical psychology. In the following, some of its basic theoretical features are briefly described and compared with psychoanalytic concepts.

Behaviorist view of addiction – the stimulus-organism-response model

Since the beginning of the 20th century, the behaviorist conceptualization of mental states and processes has been increasingly favored in psychiatry and also in addictive disorders with reference to the stimulus-response (SR) model, with the organism as a black box (or grey) box [stimulus-organism-response (SOR) model] without presupposing mental states and processes. For this basic epistemological position of analytic behaviorism/positivism[57], animal experiments in particular have provided the empirical basis for theoretical considerations. Here, we also start from this clear but superficial perspective; however, we will also criticize it in order to outline finally an ecological perspective through an onion skin-like systemic multilevel model of the situated person that takes into account a macro/micro-layering of environment and person.

Fundamentally, addiction can be characterized within a SR model as a learned extensive affinity for an object, which usually is a drug as a chemical stimulus[58]. A more theoretical definition characterizes addiction as "a syndrome at the center of impaired control over a reward seeking behavior"[59]. This implicitly assumes antagonistic forces (drivers and brakes) that determine overt behavior.

As an extension of the SOR model, the SORKC model has been successfully proposed, emphasizing the power of sustained contingencies (K) of consequences (C) [60]. In addition, classical conditioning considering contextual stimuli that become conditional stimuli and social learning through a behavioral model has been shown to be useful in understanding specifics of addiction development[61]. In treatment, all these perspectives are used as theoretical reference points for the development of therapeutic strategies. Recently, even the simple SR concept of habitual addictive behavior was successfully applied to a computer-based training to avoid alcoholic beverages presented as an image on the screen that had to be pushed away with a joystick. This training with virtual reality tools helps to balance addictive sensorimotor routines[62]. Here, we go into some conceptual details of the behaviorist approach.

Reinforcement as reward – does it correspond to pleasure?

Within the SORKC model, the occurrence of addiction is conceptually explained by reinforcement mechanisms, which represent the animal model of operant conditioning. These mechanisms are often referred to as reward mechanisms, especially in the context of neurobiology. For clinical tasks, a subject-oriented view is helpful: The (increasing) affinity to a drug can be experienced by the addicted person himself, after drinking alcohol most people experience an improvement of mood, as already impressively described by the alcohol dependent writer London[63] in 1913. In other words, the reinforcer (or reward) is experienced, in anthropomorphic terms, as a pleasant state and/or a reduction of an unpleasant emotional state. This improvement in emotional state acts as a positive feedback loop on the behavior, increasing the likelihood of its occurrence and thus "reinforcing" it[64]. Some pleasurable experiences are associated with the reduction of tension or stress. Consistent with this view, the early Freud's version of the pleasure principle[65] appears within new guise [65].

However, another question arises: Why do some drug-exposed individuals develop addiction and others do not? Is there an intrinsic risk for addiction? This question can be explained by looking more closely at the external conditions but much more so at internal conditions. For example, psychiatric comorbidity (anxiety, depression,

borderline personality disorder, *etc.*) may "drive" alcohol use, although some of these psychopathological conditions may also be "caused" by alcohol[66]. This organism-based explanation is theoretically consistent with the concept of affect regulation or stress management through drug use, and in the context of psychoanalysis of addiction, it is consistent with the complex self-medication hypothesis[67].

The cognitive turn – modeling thought cascades without a self-model?

In the experimental context, the classical SOR model was soon improved by admitting that "internal" cognitive processes and representations matter for understanding behavior, a view effectively proposed by Tolman[68] and Neisser[69]. The cognitive approach also implies that the organism must have an internal model of the external world and also of the organism itself, which will be discussed later.

In the clinical context, Beck *et al*[25] introduced the cognitive turn for almost all mental disorders, focusing on the mood-organizing power of cognitive processes[25, 70]. The cognitive model of addiction is based primarily on conscious self-descriptions: Situational perceptions, expectations (*e.g.*, of drug effects), thought processes, decision making, explicit memory, behavior planning, and other states and processing have been considered relevant to addiction. For example, in a stressful social situation, an addicted user thinks that he or she is disliked by others, with these thoughts reinforced by underlying dysfunctional cognitive schemata ("I am a loser"). These cognitive schemas and cascades of dysfunctional thinking are the targets of therapeutic intervention in CBT for mental disorders: Change in addictive behavior is targeted through changes in situational processing, cognitive coping with stress, consideration of positive and negative consequences of drinking and abstinence, *etc.*

Although a foundation of CBT is cognitive schemas, which are also associated with a concept of a self-model of the person through the notion of "dysfunctional assumptions", an explicit definition of the self/self-model is not usually used, as it is conceptualized only as a recursive (rigid) self-description of the person ("I am a loser"). In terms of cognitive schemata as a theoretical building block in CBT, there is a conceptual correspondence to the psychoanalytic concept of (dysfunctional) self-representation. In relation to this theoretical concept of self-representation, Kohut[71, 72], a pioneer in analytic self-psychology, has influentially explained drug use as a pathological narcissistic act[71,72]: The developmental non-existence of the emotional other, caused, for example, by distant parents, induces a deficient self-representation (and object representation), with the drug literally filling up these empty spaces of images (defect of the self). The drug functions as a "self-object" and contributes to psychic homeostasis. This theoretical position also makes it possible to understand the difficult therapeutic relationship in which the addicted client uses the therapist in a narcissistic mode, especially when the client is abstinent, he uses the therapist in the transference situation in a parallel mode to the drug.

Behaviorist models of self-regulation – who is the regulator?

The old notion that the drug initially serves as a regulator of the addict's affective state has also been successfully developed within the framework of learning theory and cognitive theory and can be subsumed under "self-regulation" models. As early as 1970s, some researchers such as Kanfer and Goldstein[73] and Kanfer[74] in the context of learning theory criticized the concept of stimulus determination of behavior and passivity of the person as seen in the framework of SOR model[73,74]. He emphasized the possibility of "self-management" for patients (*e.g.*, in tobacco addiction). Self-observation, self-evaluation, and self-appraisal are circularly linked process components of smoking behavior control that can be influenced by behavior therapy. This influential model corresponds conceptually with models that focus on "self-control" and "self-regulation"[75,76]. Interestingly, why and how regulation is regulated is often not clarified. From a metatheoretical perspective, these models are process-oriented and neglect to model structures of the mind. In other words, these models do not explicitly refer to the concept of a "self" or "self-model" or an "ego" operating in the loop. In contrast, within the psychoanalytic structural model, the ego is the regulator that can use drugs to relieve tensions between external reality, the id, and the superego. Moreover, in relation to the topic model, drug use can be understood as a defensive strategy of the ego to suppress or overcome implicit emotions such as anxiety, anger, and depression that occupy and deform explicit consciousness (*i.e.* "self-medication hypothesis").

The integrative power of the psychoanalytic model – translation of concepts

So far, it has been shown that some phenomena of addiction are well covered by data

and models of academic psychology, and others can be explained by psychoanalysis. Theoretical overlaps between these two approaches - for example regarding the function of the "self"– differ in the definitions and theoretical elaboration of the respective models. To achieve better integration, a combination of behaviorist and psychoanalytic perspectives might be useful, especially with regard to the heuristic significance of the assumption of drug-induced mental homeostasis based on an unbalanced mental system. An interesting special theoretical aspect of psychoanalytic models is that they are implicitly "ecosystemic" models of the mind, in that they account for multiple internal interactions of environmental feedback loops. They also appear as a kind of "ecological" model, since it is assumed that the concrete social environment of the person, namely the family into which that person was born, represents a set of factors that determine the mind. However, this (implicit) ecosystemic view also makes it difficult to identify, for example, a "causal locus of control". Is the ego too weak, is the superego or id too strong, is the self model or object model too deficient, or are the resulting conflicts too strong? Here we can only refer to some theoretical questions. (1) Regarding the conceptual connection between the reward and pleasure principle, *i.e.* mood elevation through drug use, the question arises: What are the conditions for unpleasure and/or pleasure? Pleasure is difficult to define because of the qualia problem (see first paragraph), but it can be experienced in the release of tension. Tension can be explained in systems analytical terms as the result of the clash of opposing forces such as urgent drives and behavioral inhibitions (go/no-go condition). In the context of the structural model of theoretical psychoanalysis, this description reflects the contradictory relations within and between the affective-motivational id and the repressive superego experienced by the ego. But drug exposure raises the question: Who is stronger, the driving id or the suppressing superego? From the psychodynamic perspective, drug use can also be interpreted as an additional defense strategy of and for the ego, aimed at reducing negative emotions and the experience of helplessness or powerlessness[77]; (2) A pathogenetic predisposition to addiction through the dominance of the superego was favored by Wurmser [78]. Wurmser[78] emphasized, in agreement with Fenichel, that drug-induced gratification of the infantile narcissism by removing the control of the superego is a major cause of persistent drug use. However, this model needs to be diversified in terms of the architecture of the conflicting forces: For example, the urge to work until a task is completed is usually implemented and enforced by the parents, in most cases the father. Failure to achieve these goals leads to bad feelings. Functionally, the more or less implicit idea or representation of the challenging father is a component of the superego. In addition, one might assume that the internalized image of the supportive mother allows for relaxation. However, it is important to keep in mind that the internal images of parents include more than their normative and supportive components; and (3) there is the question of where and how parents (and/or significant others) are conceptualized in SOR or cognitive models. For example, the dysfunctional assumptions ("I am a loser") are valid theoretical constructs in CBT, but the question arises as to their origin. To answer this question, it can be hypothesized that the parents' recurrent comments about the person's behavior are stored as basic reference values and as the core structure of the person's idealized self-image. This explanation of the emergence of "dysfunctional assumptions" in the context of CBT is consistent with the psychoanalytic model regarding the functional role of the superego and the self-image, which must be viewed in relation to the image of significant persons in the environment. This is elegantly captured by object relations theory and the concept of 'internal working models'[79,80]. This is currently being discussed in the context of the new theories of psychoanalysis.

Toward an integrative theoretical model of the mind

Consistent with the arguments presented earlier, we propose to design a psychological theory for psychiatry using conceptual building blocks from psychoanalysis.

In his search for the origins of human knowledge and the role of memory in our ability to experience, Freud concluded that many of human mental processes although unconscious, influence our overt behavior. In his analysis of symptoms, he postulated that each of them makes sense when one considers that important processes of the mind operate below the level of conscious awareness. Drives associated with basic needs (*i.e.* basic biological instincts) and social demands directed to the individual by the environment and context shape the person's personality, intrapsychic structures (ego, id, and superego), and mental capacities. Repeated interactions with the caregiver and other relevant persons in early childhood shape the way reality is experienced and perceived, leading to implicit knowledge and behavior patterns[81-84]. Emotional reactions that occur during interaction with others and the environment

are perceived and are more or less regulated from moment to moment. Thus, they can be transformed into signals that act as meaning markers and influence memory encoding and cognitive processing. The early social environment, such as relationships and interaction patterns with primary caregivers, influences behavior (*e.g.*, exploratory urges, attachment patterns, expression of mental and affective states). Norms and values have to be integrated; commandments and prohibitions of the culture first are mediated by the respective others; submission to them is often ambiguous and has to be worked out first in order to be tolerated without doubt[82].

Within these reciprocal experiences with the reference person and the basic environment, adaptation to reality is one of the main goals of psychoanalysis, reality being the starting point of unconscious fantasies, indicating the distinction between reality and fantasies is important for mental health and illness[85]. Psychodynamic considerations take into account subliminal signals (*e.g.*, through language, gestures, facial expressions) and latent perceptions of stimuli as well as unconscious and embodied knowledge; they aim at reshaping cognitive processing (*e.g.*, perception, attention, memory) by creating new ways of seeing and experiencing in the analytic relationship.

A framework for the processing subsystem

Taking together, these psychoanalytic issues and various cognitivist concepts used to describe the addict's internal processes, such as expectation, cognition, memory, decision, *etc.*, and also considering the importance of affective internal representations, an integrative view of addiction-related human information processing yields a systems model of the mind. This systemic model must first correspond with the symptom checklists of clinical psychiatry, which explore perception, thinking, memory, emotions, drives, *etc.* as functional elements of the mind, here linked in a basic conceptual network of the mind. Also, the concept of a self with an operational part of the ego is heuristically useful for understanding self-regulation. The important point of this model is the possibility to explain the functional relationships between these components (Figure 1)[86,87]. Since the first of these modeling attempts, several similar but partial models have been proposed in addiction theory[88,89].

The structure of representations as a reference system

In the proposed systemic model of the mind, the level of representations (or images or affective-cognitive schemas) serves as an internal reference system for further information processing, and it is also modified by this processing (EI and SI in Figure 1). It consists of three subsystems: Representations of the self, of the environment ("objects"), and of the interrelations. These representations are processed through thinking and emotional appraisal and stored in different layers of memory, so that they can function as a reference system. They are products and contents of mental processing.

In this context, it is important to emphasize that in the behaviorist view, the environment is generally conceived as the world of "stimuli": Looking more closely at the world of "stimuli", drugs (such as a bottle of beer), for example, are "salient" stimuli in the addicted person's environment, and they have an "incentive" quality for consumption. From a psycho-ecological perspective, they have a positive valence. However, the many efforts to interpret the concept of "stimulus" in the concrete "environment" of the addicted person are not fundamentally related to the trivial fact that the family (and its drug use) is the first type of social environment. The family as a system with its various elements such as mother and father and their relations (harmony, broken domestic situation *etc.*) and their relations with drugs is the framework for the child's drug use. The family exists both as an external reality and as an image in the mind, and it influences the client's experience even when parents are already dead. This issue of the contextual conditions of mental disorders was a foundation of psychoanalysis when Sigmund Freud developed his influential conceptual framework of the Oedipus conflict that, today of course, requires more subtle interpretations and clarifications. In psychoanalysis, the patient's relationships with parents are a central theme of therapeutic reflection and intervention[90].

This leads us to the heuristic value of a wider concept of "environment" that describes the surrounding world of the individual as it acts as an initial frame for behavior, for example, the family of an adolescent drug user (*e.g.*, the son): The tension caused by the incompatible relationship with the overdemanding father and the overprotective mother can lead to a chronic conflict. This conflict has two epistemic sides: It plays out not only in the psyche of the adolescent with the dysfunctional (more or less explicit) image of his parents but also in the reality as seen by the therapist (Figure 2). The experienced incoherent action structure of the parental dyad

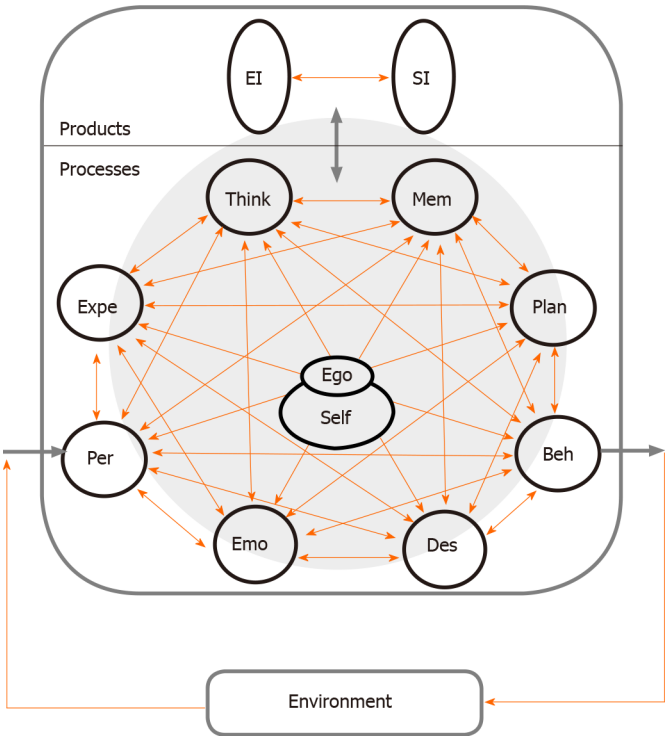


Figure 1 Visualized systems model of the mind. The list of subsystems being checked in psychiatric examination are represented here as interconnected mental operators (subsystems) within an operationally closed network. Consciousness is represented here as a shaded circle, regarding the metaphor of light and dark. Not all relations, especially of the ego/self, are depicted here in detail[88]. Perc: Perception; Expe: Expectation; Thin: Thinking; Mem: Memory; Plan: Plans of behavior; Beh: Behavior; Des: Desires; Emo: Emotions; EI: Environmental image; SI: Self-image as affective-cognitive schemas.

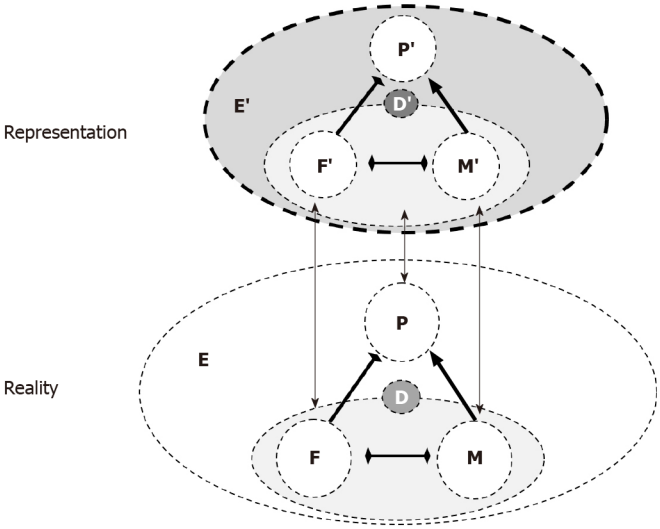


Figure 2 Model of reality and affective-cognitive representation of the adolescent drug using person (P; D, drug) and his or her family as the environment (E): The demanding father (F, with line with transom) and the supporting mother (M, with arrow) induce tension for the child that results in drug consumption for sedation and/or escape. In addition, the parents oppose each other (line with two transoms). The model depicts the reality (E, P, F, M, D) and the mental representation by the patient (E', P', F', M', D').

may be an important trigger for drug use. Consequently, the family structure of the young drug user is one a very important topic for therapeutic exploration.

However, in line with this theoretical and practical insight, the term "environment" needs to be more differentiated, as the adolescent drug user is involved in other environmental subsystems: His peer system, the world of school, the leisure space, the community, the internet, *etc*. In other words, not only the family but the whole "ecology of the drug user" has to be explored by the therapist[91]. This complex relevance of the term "environment" (and relations) demands some deeper meta-

theoretical consideration.

"ENVIRONMENT" – ORDINARY LINGUISTIC TERM OR PHILOSOPHICAL CONSTRUCT?

The theoretical importance of a solid conception of "environment" is not sufficiently considered in psychiatry. As for biological reductionism in psychiatry, the goals of environment-related research also exhibit some conceptual and epistemological simplifications that are misleading. Surprisingly for biologists, the use of the term "environment" in biological psychiatry usually is mostly based on a very vague meaning of everyday language: For example, in the extremely important gene-environment interaction studies 20 years ago by Caspi *et al*[92], "environment" is operationalized only by stressful situations, such as childhood maltreatment, mainly by the family[92]. These conceptual shortcomings can also be observed in RDoC as will be explained later. Interestingly, it neglects a very important epistemological distinction that emerged more than 100 years ago in the context of the history of biology (and ecology/environmental science): (1) The objective environment as seen by the remote researcher; and (2) The subjective environment as experienced by the immediate living being.

If we briefly concede at this point that "objective" is shorthand for the sophisticated scientific observation reported through data and "subjective" is the phenomenal appearance reported verbally, we think that this categorical dichotomy is at least workable in practical psychiatry, although "objective" is not an epistemologically grounded category from a constructivist point of view, since scientists are also subjects and can only represent a methodologically grounded "intersubjectivity". From a pragmatic point of view and for a clinical psychiatrist, a very important challenge in the diagnostic phase is to compare intersubjectively, together with the patient, the objectively observable (and possibly data-based) situation with the subjectively experienced situation, in order to identify a paranoid processing of the surrounding world.

Interestingly, a pragmatic dichotomy of objective/subjective is also important in human biology as it partly reflects a difference between natural science (molecular biology) and sciences of the mind or phenomenal self-awareness (phenomenology). This problem of a double methodology corresponds to the philosophical qualia problem beautifully formulated by Thomas Nagel: "What is it like to be a bat?"[93]. This question deserves closer consideration here.

Biology and ecology – the physical environment and the sensorimotor loop

In ecology as the science of the relationships between environment and organism, environment is a crucial concept. Consequently, it must to be emphasized that Ernst Haeckel, the founder of academic ecology, defined environment as the "surrounding external world" (or "the surrounding external space") of an organism, referring mainly to the physical-chemical environment[94]. From a philosophical point of view, this position is associated with a positivist, empiricist, objectivistic, reality-based view. In contrast, but independently, Jakob von Uexküll's environmental theory ("Umweltlehre") focused on the informational realm, namely the perceptual and effectual world surrounding an animal, and emphasized that organisms only selectively receive environmental stimuli, a subset which he called the "Merkwelt", and that organisms can also only selectively act on the environment, a subset which he called the "Wirkwelt"[95]. With his analysis, Uexküll elaborated the importance of subject-centered attribution of meaning to the external world and so is thus considered the founder of biosemiotics. In this respect, this view was also called "phenomenological biology" or "subjective biology", which means that the term environment only makes a functional analytical sense, when it is related to information processing properties of the respective living being. In line with this view, Uexküll completed the picture by connecting "Merkwelt" and "Wirkwelt" through the model of a "functional circle" constituting organism-environment interactions. This kind of concept emerges in phenomenology and ecological psychology reducing the gap between the "outside" and the "inside", leading to a kind of circular psychology by emphasizing the operational closedness of information processing and generation.

Psychology – the informational environment /world

The aforementioned dichotomies of "internal" and the "external" or "subjective" and

the "objective" in early ecological psychology (or psychological ecology) were essentially reflected in critical controversies between Kurt Lewin[96] and Egon Brunswik[96,97]. Brunswik[97] emphasized the external world as it is perceptually screened by ecological sampling, while Lewin[96] focused on the topological structure of internal representations of the world that he called "habitat". Certain subsets of the habitat exert a field-like "valence" on the person, but barriers may oppose this appetitive disposition and behavior. Later, James Gibson[98,99] proposed a hybrid conception that assumes that perception of the world depends on action, and action depends on perception of the world, a circular model similar to Uexküll's functional cycle[98-100]. In his dynamic view, the perceived image of an object is the still frame of a movie created by movements (*e.g.*, of the eyes and/or the person). The cues of the physical world as its significant stimuli during movement are vectors that are processed by the sensory system, looking for invariants in the low of stimuli, resulting in images such as "gestalts" as discussed by Gestalt psychologists. Gibson[98,99] also understood the external visual world as a "stimulus array" that acts on the human subject as "affordances" by and for intentional actions of the person: The structure of a chair becomes visible through the by exploration of this object and then it "offers" the possibility to sit down.

Gibson's work can serve as a reference for new phenomenology that emphasizes the intertwining of the individual with the world as proposed in the anthropological concept of the person as an embodied, embedded, extended, and lived mindful being [101,102]. Interestingly, the conceptual bridge from the physiological sensorimotor level to social psychology has a long tradition of discussion in the context of ecological psychology[103].

Sociology – the textual and communicative world as the social environment of actors?

The "social environment" is only implicitly touched in RDoC through the category of "social function", a domain exemplified by social dominance, affiliation/separation, identification of facial expressions, self, *etc*. It should be measured by self-disclosure and behavioral analysis but also at the genetic, molecular, cellular, circuit,, and physiological levels. The social conditions of mental states and mental processing-family integration, socioeconomic class, educational level, social support, *etc.* are important, however, because social functioning requires a certain level of social integration and vice versa[104]. In addition, urbanization, migration, neighborhoods, unemployment, group membership, ethnic diversification, gender issues, *etc.* are also issues that are rarely explicitly considered by the biological perspective of RDoC.

Obviously, these categories are not essential in RDoC, and it seems that social theories are not covered by RDoC. For example, social anomie, lack of social resonance, and similar aspects of social order and social relations are not explicitly included for study. By construction, RDoC seems to underestimate the top-down causality (and reciprocal bottom-up causality) of individual behavior through social rules[105], the influence of social structure on action[106,107], *etc.*, which are at least mediator or even moderator variables of mental health.

But what does "social" mean? It is important to note that in modern sociological theory, the social as an epistemic object is more than the population; it is a set of operations (actions) and rules that relate to interpersonal and interinstitutional domains[107]. "Social" also means a culturally specific definition of norms, values, beliefs, *etc.* by which someone functions. In turn "functioning" means performing a social role, especially in the context of organizing a social system, institution, social space, or behavioral setting (see below). In the context of psychiatry, the term "social" in most cases refers to the micro-level of interpersonal interaction and communication as the object of knowledge, while on a mesosocial level, groups and organizations are the object of social scientific investigation that finally, on a macro-level, also analyzes society and its social subsystems such as science, law, religion, economy, state, politics, *etc*. In other words, one must admit that individuals exist in the context of multiple social systems (*e.g.*, economics, law, science) and are confronted with institutions through rules of action: To pay or not to pay, to be right or wrong, to be true or false in relation to socially defined "reality", *etc.* The consecutive relations between the individual and the social environment mean integration or exclusion: If I cannot pay I cannot participate, if I am wrong I must accept punishment otherwise I will be excluded by imprisonment, *etc*. A society based on the rule that everyone is responsible for his own destiny would not organize public support systems for marginalized people (*e.g.*, the chronically mentally ill), who more and more exhibit a multiple downward spiral to homelessness. In general, the top-down modulation of

individual behavior by macrosocial concerns is seen as a systemic colonization of the individual lifeworld[108].

As a methodological consequence, the social domain can be explored analytically but only on a multivariate correlational basis and not seriously on a causal level. In accordance with this methodological limitation, social neuroscience should compare electroencephalograms and other biomarkers of subjects belonging to society with a strongly state-controlled economic order with the question: Is there a correlated difference (covariance/variance analysis)? And if so, can it be ruled out that there are other factors such as biological or psychological (and micro-social) variables that cause this difference?

There is another more profound methodological problem in social science that has already been addressed: Categories of the social can be measured objectively to some extent, as empirical social science does, but for behavior the subjective side is more important: How do I experience the world? This subject-centered view was already fundamentally emphasized by the philosopher Husserl[109] who constructed the subject-centered concept of a world view he called "lifeworld"[109], which was further developed especially by the Austrian sociologists Schütz and Luckmann[110,111], Berger and Luckmann[112], and also Habermas[113]. Another influential approach in sociology, namely the work of Bourdieu[114-116], must be considered. Bourdieu[114-116] conducted empirical studies in Algeria and developed new theoretical categories to describe the context of social behavior (*e.g.*, concepts such as "social space" or "social fields"). Interestingly, Bourdieu[114-116] acknowledges an objective social reality and not only its constructedness by the subject and society, as constructivists often see it. In relation to psychiatry, cultural psychiatrists also noted, that "culture is in the head/brain/mind and in the environment"[117]. The "social" in psychiatry is a social reality.

However, there is another side to the "social" in psychiatry; practical clinical work requires close collaboration with social workers to optimize service to patients. Consequently, knowing how social workers think, *i.e.* the theoretical background of social work, is useful. Social work theory is mainly based on aforementioned concept of the "lifeworld" model derived by Husserl[109,118,119] and is often associated with Bronfenbrenner's[120] approach to psychology[120]. This is another good reason to differentiate the concept of "environment" in the context of psychiatry.

Towards an integrative taxonomy of the term "environment"

Looking back at this section on the different aspects of the concept of social environment and in terms of its essential importance for mental health, the distinction between the physical environment facing climate change and the digital environment with its virtuality and the machine-based technical environment (*e.g.*, robots) should also be made clear. Moreover, the "natural" environment (and its hazards) may be an interesting field for psychiatric research. In other words, an explicit taxonomy of the term "environment" is useful, similar to that used in ecological (and environmental) psychology. These semantic distinctions imply a holistic concept of environment that also covers the heterogeneity of topics mentioned earlier. Interestingly, almost no biological psychiatrist refers to ecology, which is a biological field of research and had a strong influence on sociology and (psychiatric) epidemiology in the first half of the 20th century. Perhaps in the context of studies of "urbanity" and mental health, there is a revival of the ecological view[121]. With the aim integrating these different meanings of the term environment, we present an outline of a comprehensive conceptual framework for a more precise use of this term, which is already useful in the context of ecology and sustainability science.

First, it is important to recognize that the general term environment also includes semantically similar terms in the scientific context, such as environment, "context", "setting", "behavioral setting", "social space", *etc.* These terms have specific meanings, but they share a common semantic stem, namely the "external" (or "surrounding) world. From a systemic perspective, the external world is a system of elements that are related to each other and to the living being as observer and actor. These elements are often referred to as "factors", "dimensions", "areas", "levels", *etc.* However, there is no universally accepted convention on the taxonomy of these concepts. Moreover, there are no interdisciplinary accepted definitions and/or conceptual explanations of these terms. Here are some semantic diversifications that can help clarify meaning when "environment" is used in interdisciplinary communication[122].

Basically, it has to be taken into account that the distinction between system and its environment is a (physical) distinction with a more or less concrete boundary structure (skin, membrane, entry rules of a social system) that constitutes the system. At the very least, the observer of the system must construct a conceptual distinction. This

issue has been widely discussed in systemic family therapy[123] and sociology[124]: A system constitutes itself by constituting and/or enforcing or extending its boundary structures.

Consequently, the categorical and real distinction between system and environment implies the notion of a "relation" (*e.g.*, a boundary relation such as inclusion or exclusion mechanisms or rules) between a social system and its environment. From a cell biological point of view, this difference is established up by the *membrane* with its ion channels and its gating and ion pumps that "establish" the difference between the external and internal environments. Psychologically, objects of the environment have an attraction, a valence, or an affordance (or a repulsion) for the person. This disposition is often meant when one uses the very general term "relation". However, this term deserves further analytical consideration, which can only can be touched upon in the final section of this paper.

If we summarize these semantic aspects of the term "environment" in a preliminary taxonomy, we can highlight some points (Figure 3): (1) The distinction between "objective environment" and "subjective environment" is necessary because it has already been figured out (*e.g.*, measured and/or experienced air temperature). It is an everyday experience of any self-critical person acting in a social context. The history of scientific discussion in psychology and sociology also shows that this distinction is irresolvable. Philosophers distinguish the objective "third person perspective" and the subjective "first person perspective" and emphasize that the subjective experience precedes the scientific view of the external world; (2) The temporal dimension is evident in the heuristic usability of the concept of "past", "present", or "future" environment. The developmental ecological psychologist Brofenbrenner[120] proposed the concept of a chronosystem representing the significant ecological transitions when a child becomes an adolescent, an adolescent becomes an adult, a student becomes a researcher, *etc.*; (3) As for the objective side, the external environment is primarily a spatio-temporal world, that can be described in terms of physics and other natural sciences, but perceptual Gestalt psychology has shown for decades that the experienced world is also the result of constructive processes of the subject and the society. Construction is not possible without elements, so for the construction of an image (Gestalt) of an object of the world, the constitution of relations of its elements is essential. In line with this spatial dimension and in a systemic view, the distinction between a micro-level (family, work, and school), a meso-level (community), and a macro-level (society) has been influentially emphasized by Bronfenbrenner[121]. The microsystem is primarily understood to be the family, but the school or workplace, the recreational sphere, and other sub-areas of individual's living space are also addressed by this level. The meso-environment (or meso-system) is the summary of these micro-environments. The meso-level is embedded in the macro-environment of the society, which is referred to as the macro-system. Bronfenbrenner also introduced the notion of the exo-system, which influences the person but that in turn cannot be influenced by the individual; (4) Entities: With this term we propose to distinguish between material-energetic or physical *vs* immaterial (informational) environment. In addition, scientific ecology distinguishes other sub-entities, such as inanimate natural (abiotic; soil, water, air), animate natural (biotic; microbes, plants, animals), technical, personal, social, cultural, *etc.*, environment. The everyday understanding of these terms is sufficient here, but a precise definition remains difficult, especially since there is currently no philosophical ontology (see above); (5) Spheres of life: Lifeworld, work world, *etc.*, are environmental domains that are distinguished according to their functional importance for people. They are separate but partially overlapping spheres of life that are concerned with these issues (home office); (6) Qualities: Environmental characteristics can be classified as "good" or "bad" in relation to the environmental effects experienced by the person (attraction, repulsion); (7) Quantities: These environmental properties can be represented, for example, as the density of the respective environmental elements occurring in the space-time framework. A stimulus-rich world may trigger stress in a busy person but may also be perceived as pleasure by a bored individual; and (8) Effects and their directionality: Impacts, effects, and interactions are corresponding categories.

This taxonomy should not be understood as a rigid framework but as a reference for important specifications and distinctions in interdisciplinary communication; the communicator should define what he or she understands by the chosen term.

This taxonomy can also serve as a guide for the term relation. Although in the context of psychiatry one usually means "social relationships" by this term, relationships can be observed objectively/subjectively at certain times, at different levels (micro/macro), in terms of physical or interpersonal dimensions or domains, in

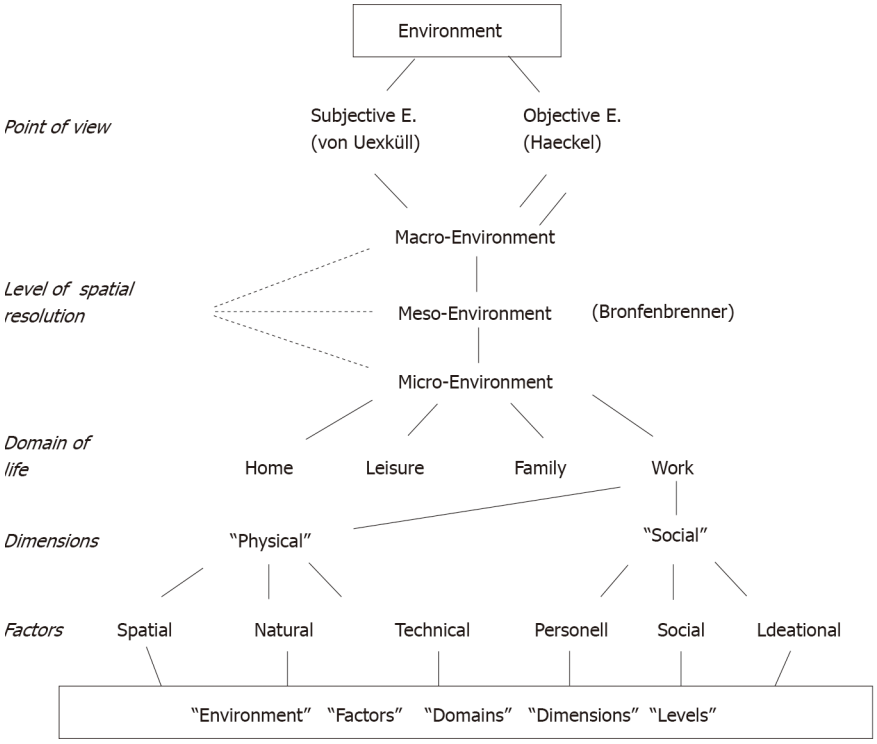


Figure 3 Conceptual taxonomy of environment-related and partially interchangeable terms (details see text).

terms of lifeworlds (work *vs* leisure domain) and the experienced quality and quantity *etc*. This will be revisited in the next section, where we outline the ecological perspective in more detail.

CONTOURS OF A NEW THEORETICAL FRAMEWORK – "ECOLOGICAL PSYCHIATRY"

We now we try to put together the things that have been distinguished before and propose a sketch of an integrative conceptual framework of a human ecological perspective, which has some cross-disciplinary traditional roots but is not yet really established in psychiatry and is also only rudimentary in medicine: (1) The first section has shown that psychiatry lacks an area that can be called a "theoretical psychiatry" and that the methodological plurality needs knowledge integration as it was proposed by the bio-psycho-social model. It is believed that the best basis for a general theory of psychiatry could be the modern psychoanalytic theory, especially since it is currently elaborating its roots in neuroscience[125-127]. Moreover, the last fundamental theoretical developments in psychoanalysis that led to in modern object relations theory could be a fruitful basis, also for an ecological perspective; (2) The second chapter on addictions showed the usefulness of the behaviorist approach but also highlighted the heuristic relevance of psychoanalytic thinking and modeling, where "relationships" are the key issues, even if its therapeutic relevance sometimes only comes into play at a later stage of treatment. Using the clinical example of adolescent drug addicts, it was emphasized that the family, as the most important social environment, has always been a constitutive theme of psychoanalysis. Thus, psychoanalysis per se has always been a bio-psycho-social approach; (3) In the third section, the semantic complexity of the term "environment" was pointed out. This chapter also pointed out the theoretical disparity of the "environment" when considered as a set of stimuli and/or as the family; and (4) Taken together, these issues imply a conceptual framework based on a differentiated but integrated model of human-environment relations as a system that is provided by the human ecological approach. But what exactly is "ecology", and what are constitutive concepts?

The human ecological framework in psychiatry – knowledge and theory integration

As mentioned earlier, ecology as a biological science was founded by Haeckel[94] in

1866 and was defined as the science of the relationships between organisms and their surrounding environment[95]. For a time in the 20th century, this approach, which aims to understand human living systems, had a major influence on disciplines such as sociology, geography, psychology, epidemiology, *etc*. Several very general calls for a systemic ecological perspective have also been published in psychiatry[128-130]. In a similar vein and in relation to clinical issues of addiction, an ecosystemic multilevel perspective was proposed in the 1990s under the name "Ecology of Addiction"[92]. Following this, a generalization as "ecology of the person"[131] has been published and recently further elaborated[122]. This corresponds with the call for a "neuroecology"[132,133] or even for an "ecology of the brain"[134].

Rooted in cultural psychiatry, Kirmayer and Crafa[21] recently proposed an "ecosocial psychiatry"[21]. Emphasizing the need for a "new science of psychiatry" he argued: "A multilevel, ecosocial approach to biobehavioral systems is needed both to guide relevant neuroscience research and to ensure the inclusion of social processes that may be fundamentally contribute to psychopathology and recovery"[135]. This approach has been used as a basis for the development of a new science of psychiatry.

As a result, we propose here a person-centered and environment-centered view in psychiatry that considers the patient as a "situated subject". We also propose a multilevel systemic view of mental disorders that focuses on the mind as an information processing subsystem. This systemic ecopsychiatric perspective appears as the logical integration of the current counterproductive divergences between research and practice.

In this sense, and in relation to addiction, a first step of theoretical integration seems to be possible by linking the psychoanalytic model not only to CBT, but also to the ecological psychology of Lewin, Barker, Gibson, and Bronfenbrenner, by linking it to the "ecology of the mind"[136] and the phenomenology of the embodied, embedded, expanded, and performed subject[137]. These efforts could lead to an "ecology of the person" that offers more coherent options for understanding disorders and planning their treatment and prevention[131].

With this in mind, we want to move toward a human ecology view of mental disorders based on the previous sections of this paper: We will propose three conceptual building blocks – the anthropological concept of the person, the ecological concept of the environment, and the analytical concept of the term "relationship".

The person

The person can be described in a multidimensional framework, for example, when it comes to the clinical context[122]. In clinical psychiatry, about eight basic dimensions are usually checked: Time (When were you born?), space (Where do you live?), physical state (Are you physically well?), mental state (How are your memory functions?), linguistic competence (How can you describe your feelings?), social domain (Do you have a relationship?), cultural aspects (Religious belief?), and economic status (Are you employed?). This information provides a treatment-relevant framework of the situated person and is not theoretically integrated.

The "environment"

The complex meaning of this term has already been discussed at length. Related to basic clinical practice, as highlighted above, five of the above questions deal with the person's environment: The temporal, the spatial, the social, the cultural, and the economic. These are some essential dimensions of the surrounding world that determine the manner and quality of the persons' existence, with implications for health status.

The relations

The categorical distinction between the person and her environment is counterbalanced by the concept of the relations: A relation is basically conceived here as a disposition between two elements that is recognized by an observer, such as a doctor in a clinic or the subject or the researcher: What are the subject's relations with his or her parents? In this construct, too, the first essential distinction is the epistemological one, between the "objective" relationship as seen by the expert and the "subjective" relationship as seen by the patient. Although there are varying degrees of realism within the views, which may even be paranoid in nature, these dichotomous distinctions are pragmatically useful here. The relations of the internal and external psychosocial environmental relations between the person and their environment in terms of affective-motivational values must be optimized in therapy. Consequently, the occurrence of objects (persons) in the environment that are similarly structured to

the reference objects of the representation evokes old patterns of cognitive-affective processing.

Although a similarly detailed analysis of the concept of relations as shown in this paper for the concept of "environment" is necessary, the issue of relations is already addressed essentially in object relations theory[80,138,139]. It is the affective valence of relations (or the quality of affects) that causes the appearance of environmental objects. It is, of course, co-determined by the sociocultural context. The system of relations as a "structure" of the representational system of the object and the subject and their interrelations can be distinguished in a simple but more systematic way: The relations of the person to the environment can be classified as processes and thus with "fugal" and "petal" directionality: The giving and the taking. In the abstract mathematically oriented terminology, the taking is often preceded by a demanding, and if a giving is not accepted it is a refusing. The content of the relationships, the entity transferred, for example, information, matter/energy or love, support, *etc.*, is central (Table 1). These framing concepts have not yet been translated in this form into the psychoanalytic terminology. Interestingly, they have some roots in the social psychological school of exchange structuralism[140,141]. Although developed in the context of economic studies, they can also be used to describe interpersonal interaction within the family: The father demands performance from the child and thus has a demanding image for the child, the mother supports the child and has a supportive image for the child. As a result, the polarized image of the "bad father" and the "good mother" emerges and solidifies as object representations with their respective emotional charges. In other words, the content of the actions or the (verbal) signals of the relationship can be categorized as acknowledgement, care, support, commitment, *etc.* Thus, intrafamily interaction and the structure as the essence of interactions can be described in a naturalistic way through ordinary language that can be easily documented in psychotherapy sessions (Table 1). The psychopathological relevance is that in every interaction, not only an intertemporal balance of the integral of interpersonal give and take but also of intrapersonal give and take must be established to produce harmony and avoid conflict, which in any mental disorder are at least accelerators of pathogenetic mechanisms.

This notion of balance and imbalance of interactions is in turn linked to the well-known and highly integrative and heuristically fruitful concept of stress.

Stress as a central construct – an ecological conceptualization

A relation theoretical framework for stress theory can be reconstructed through an imbalance of four relations between needs (desires) and competencies of the person and offers and barriers of the environment: (1) The person's needs (desires, demands) in relation to their (2) competence to satisfy these needs depends on the (3) environment's offers in relation to these needs, and in relation to the (4) environment's barriers. For example, related to the person: I want roses in my room (desire), because roses are beautiful (offers), but they have thorns (barriers). If I have a tool (competence), I can cut them and put them in a vase at home.

Although this concept could be elaborated further, this example is meant to illustrate the ecopsychological perspective. A relational stress concept is also appropriate at the biological level: The probability of an infectious disease is determined by the relationship between the infectivity of the pathogen agent and the vulnerability of the host and their respective embeddedness in their environments.

Seen in this light, the fruitful bio-psycho-social conception of the stress paradigm can be combined with an ecological perspective, including for a relational/ecological understanding of addiction.

CONCLUSION

For a comprehensive picture of mental health, the constitution of a "systemic ecology of the person" is crucial. Within this theoretical project, the interdisciplinary reconstruction of the concept of "relations" seems to be essential. The focus is on the quality of the relation between the person and the (social) environment, as they are conceptualized by various theoretical approaches/constructs such as "vulnerability", "resilience", "salutogenesis", "risk factors", "protective factors", "affordances", "asymmetries", "barriers", "incongruences", "attachment", *etc.* Psychoanalysis, especially object relations theory, has a rich repertoire of descriptions of these relational terms[140]. Finally, the relationship between the subjective perspective ("I am observed by secret service") and the objective perspective on the world ("there is

Table 1 Exchange forms and contents–some basic examples

Give	Content	Take
Give out	Rejection	Accept
Spend	Money, time	Receive, consume
Give away, devote to	Burden	Accept
Offer	Care	Demand
Give	Money	Accept
Give away	Furniture	Accept
Send	Information	Receive

very likely no interest of secret service") is a crucial issue for psychiatrists and psychotherapists to work on.

It is important to conclude this paper with the position of Kirmayer and Crafa[21]: "This ecosocial view of mind, brain, and culture calls for a shift in perspective from a psychiatry centered on brain circuitry and disorders toward one that recognizes social predicaments as the central focus of clinical concern and social systems or networks as a crucial site for explanation and intervention."

ACKNOWLEDGEMENTS

We thank Dagmar Steinmair for her help in editing.

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World Journal of Psychiatry

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World J Psychiatr 2021 November 19; 11(11): 937-953

DOI: 10.5498/wjp.v11.i11.937

ISSN 2220-3206 (online)

EVIDENCE REVIEW

Therapeutic termination of pregnancy and women's mental health: Determinants and consequences

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Author contributions: Pessina R and di Giacomo E wrote the paper; Rucco D, Colmegna C, Santorelli M, Placenti V, Aliberti F and Clerici M collected data; All authors analyzed papers and approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Country/Territory of origin: Italy

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

The therapeutic termination of pregnancy (TToP) is an induced abortion following a diagnosis of medical necessity. TToP is applied to avoid the risk of substantial harm to the mother or in cases of fetal unviability. This type of induced abortion is provided after the second semester of gestation if fetal illness or the pregnancy cause physical danger or pathological mental distress to the mother. Socio-cultural and economic determinants could influence the desire for children and family planning in couples, as well as the use of effective contraception and the choice to perform an induced abortion. Also, pre-existing mental health problems could affect the decision between carrying on a problematic pregnancy or having TToP. Furthermore, the TToP is a reproductive event with an important traumatic burden, but also with an intrinsic therapeutic effect and it can produce different psychological and psychopathological effects on women and couples. The aim of this review is to evaluate what demographic, reproductive and psychopathological determinants are involved in the choice of undergoing a TToP in women. Also, we will examine both positive and negative consequences of this procedure on women's mental health, underlying which factors are related to a worse outcome in order to provide the best clinical support to vulnerable groups.

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Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: July 15, 2021
Revised: July 27, 2021
Accepted: September 14, 2021
Article in press: September 14, 2021
Published online: November 19, 2021

P-Reviewer: Kaur M, Liu X
S-Editor: Ma YJ
L-Editor: A
P-Editor: Yu HG



Key Words: Therapeutic abortion; Women's health; Depression; PostTraumatic stress disorder; Perinatal care; Psychiatry

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Core Tip: The choice of having a therapeutic termination of pregnancy (TToP) is strictly personal and several demographic and reproductive factors may contribute. Women who have a TToP are more commonly affected by a previous mental disorder, which influences their mental outcomes after it. There is a higher prevalence of any axis I psychiatric disorder in women who choose for a TToP, but the correlation with personality disorders has been less examined. TToP seems to produce both positive and negative psychopathological effects on women and only a minority of women show psychiatric disorders after it, especially those with a previous psychiatric history.

Citation: di Giacomo E, Pessina R, Santorelli M, Rucco D, Placenti V, Aliberti F, Colmegna F, Clerici M. Therapeutic termination of pregnancy and women's mental health: Determinants and consequences. *World J Psychiatr* 2021; 11(11): 937-953
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/937.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.937

INTRODUCTION

The therapeutic termination of pregnancy (TToP) is an induced abortion following a diagnosis of medical necessity. TToP is carried out to avoid the risk of substantial harm to the mother or in cases of fetal unviability. The TToP, according to the Italian Law 194/78[1] and different legislations around the world[2], is provided after 90 d of gestation if fetal illness or the pregnancy may cause physical danger or pathological mental distress to the mother. Unlike voluntary termination of pregnancy (VToP), which is performed on women's request, TToP requires a clinical evaluation by a physician.

The choice of undergoing a termination of pregnancy (both voluntary and therapeutic) is strictly personal and complex for the woman and the couple since numerous factors are involved in the decision-making process.

Furthermore, TToP is an obstetric event with an important traumatic burden, but also with an intrinsic therapeutic effect. This review aims at evaluating the demographic, reproductive, and psychopathological determinants and the psychiatric consequences of TToP in women and couples.

DEMOGRAPHIC AND REPRODUCTIVE DETERMINANTS OF TTOP

Several socio-cultural and economic determinants influence the desire for children and family planning in couples, as well as the use of effective contraception or the choice to have abortion in case of unwanted pregnancy or maternal physical or pathological mental distress. Many studies do not discriminate between therapeutic and voluntary ToP when analyzing possible demographic and reproductive determinants, thus introducing a bias in understanding decisional pathway of TToP.

Maternal age

In Western countries[3,4] the rate of TToP is higher in women aged between 20 and 34 years old. That timeframe correspond to the period of greatest female fertility rate, when it is more likely a woman gets pregnant and may wish to have an abortion in case of newborn illness or unwanted childbearing.

Instead, the relative rate of TToP compared to the total number of pregnancies by age group appears to be doubled in women aged under 20 years and over 34 years[3,4]. In fact, in extreme maternal ages, there's a lower female fertility rate, but also an increased risk of genetic fetal diseases or congenital malformations, which could explain the higher risk of TToP.

Different but not conflicting results were observed in developing countries, such as Ethiopia[5] or India[6].

In the Third World, maternal age at first pregnancy is significantly lower than in Western countries and most of the female population requiring abortion is under the age of 34 (89.5%)[5]. Furthermore, most of the voluntary terminations of pregnancy are performed in women aged 20-24(34%) and 15-19 (24%)[5,6].

Several studies[3,7,8] show that adolescent women have abortion later in pregnancy than other women: this could be due to late pregnancy discovery and existing social, economic, and legal difficulties linked to that group.

Marital status

In Western countries, the frequency of TToP is 3 times higher in women who are divorced than in unmarried and 5 times higher than in married or widowed[3,9].

The choice to undergo an abortion seems to be strictly conditioned by the absence of a partner, a close marital bond, or a supportive family unit, also because divorced or unmarried women seem to be more inclined to unwanted pregnancy, VToP and TToP [3,9].

The couple relationship is often an important decisional determinant of TToP in women; as demonstrated by Chibber *et al*[10] the three most common partner-related reasons for having a TToP are: (1) A poor relationship between the two members of the couple; (2) Male partners unable or unwilling to support a child; and (3) Partner's personal traits that make them unsuitable to be a father.

In developing countries, the majority of women who decide to have an induced abortion are married (46.4%) or single (41.6%)[5], probably because in many of these countries single-parent families and divorce are not culturally accepted, despite being legal.

Women's level of education

Several studies[3,7] from the Mediterranean area show a direct correlation between women's level of education and termination of pregnancy: women with a high level of education (secondary or university degree) show a rate of TToP 10-15 times higher than subjects without any school qualification.

However, in the Northern Europe[8,9] and Australia[11], higher rates of TToP were observed in women with a lower cultural level, which is more often associated with lower wages and a lower socio-economic level.

In developing countries, such as Ethiopia[5], the majority of abortions are performed on illiterate women (30%) or with education under 8 years (23%), while only 9% of TToP are performed on women with a diploma or university degree.

In India[6], instead, women with higher levels of education show a lower fertility index, because education strongly influences women's attitudes towards pregnancy and family size, leading to a decline in the desire of numerous offspring. At the same time, educated Indian women tend to avoid sterilization practices and have an increased risk of unwanted pregnancy for more liberal sexual behavior. Additionally, educated women are more likely to accept reproductive control and induced abortion than poorly educated or illiterate women.

Women's employment

The rate of female workforce affects the demand of induced abortion in a country, because working women, overall, have more control over their family planning and reproductive lives thanks to their economic contribution[6]. In fact, in Western countries, employed women have an absolute frequency of TToP almost two times higher than housewives and students. On the other hand, considering the relative frequency of induced abortion with respect to the fertility index, students show a double rate of abortion compared to both employed women and housewives[3,9,12]. This huge gap is due to the fact that female students do not have their own income and this leads them to decide they do not carry on an unwanted pregnancy.

Women with the lowest monthly income are those with the greatest use of abortion: in the United States[13] women with an income below 100% of the federal poverty level (FPL) have an abortion rate 5-6 times higher than women with a double income. A similar correlation was also observed in other European countries[7,9,14].

In developing countries[5,6], the use of abortion is greater in housewives (37%) or schoolgirls (27%), while only a minority of women requesting TToP are employed. Moreover, women with the lowest monthly income (< $ 26.3 per month) are the majority of requesting induced abortion (78%). Importantly, in those countries the effect of female occupation on reproductive behavior depends on women's kind of job. Women employed in agricultural or industrial settings show a lower rate of induced

abortion, due to their possibility of carrying on pregnancy and raising children[6].

Number of children and family planning

There is a direct correlation between the number of children in the family and termination of pregnancy; women with several offspring (2 or more children) show an abortion rate 5 times higher than women who have no children or only one[3,12]. Furthermore, family planning (assessed as the woman's referral to a family planning clinic in the previous months) seems to be inversely related to the choice of having a TToP[12]. Uria and Mosquera[3] showed that 60% of women with an induced abortion did not refer to a family planning clinic in the previous 2 years. A similar rate of unplanned pregnancies ending in TToP or VToP was observed in developing countries [5].

Interestingly, the percentage of adolescent women who have an induced abortion without family planning rises to about 80% and this highlights the need for sex education programs to prevent unwanted pregnancy and other sexual issues in that fragile population[3].

Urbanization rate

In developing countries[5,6] and Australia[11], the frequency of TToP seems to be higher in urban than in rural areas, considering the widespread availability of health services in towns.

Possible reasons for correlation between urbanization rate and induced abortion are well explained by Bose *et al*[6] in their study from India. In India, urban residency appears to promote an anti-natal lifestyle and increased cost of having children. Children in urban areas are more difficult to supervise and are less economically productive than in rural places since they cannot be employed in agricultural work. This leads women from urban areas to wish for less children. Furthermore, the social norms that promote small family sizes and the government's family planning messages are more easily spread in cities thanks to a better access to the media (TV, radio). Thus, women living in large cities are more likely to perform a termination of pregnancy not only for their desire for smaller families but also for an increased knowledge and access to legal abortion services.

Immigration

Rasch *et al*[9] showed that immigrant women are a vulnerable group with an increased risk of unwanted pregnancy and induced abortion due to their social and economic condition. Nevertheless, in a recent reanalysis of data from Mortensen[15], authors showed that immigrant women had a 2 times increased risk of induced abortion compared to non-immigrant women with the same monthly income. In addition to these findings, the study by Pérez *et al*[16] has shown that, in Spain, termination of pregnancy is more common in areas with a huger concentration of immigrants from outside the European Union. The authors suggest that the status of "immigrant citizen" is an independent variable that must be taken into account in evaluation why a woman may choose for abortion[15].

Women's ethnic group

In the United States, women belonging to ethnic minorities may experience an increased need and reduced access to health services for induced abortion than white women, being thus exposed to negative medical and social consequences[13,17-21]. The disparities in abortion rates are well documented, with rates of 1.1% in non-Hispanic white women, 2.8% in Hispanic women, and 5% in black women. Furthermore, although pregnancy are unplanned in 51% of all American women, the percentage rises to 70% in African American women and 57% in Latin American ones, compared to 42% in white women[13,17]. Those differences are confirmed in multivariate analysis, net of age, and monthly income, suggesting that ethnicity is an independent risk factor for having a termination of pregnancy.

Data showed that Hispanic and Black women are also more likely to have termination of pregnancy at a later gestation age (from second trimester onwards) than white women. Authors justified[13,17] an increased abortion rate in ethnic minorities in the United States with lower socio-economic status, higher level of stress and precarious working/housing conditions, less common use of effective contraceptive devices, lack of health insurance coverage, and the absence, in many American counties, of accredited health care facilities for termination of pregnancy .

Although studies[17,19,20] have focused on African and Latin American women, a higher abortion rate has also been described in other minority ethnic groups such as

Indian Americans, Alaskan Natives, Asians, and Pacific Islanders[13].

Religious beliefs

A strong religious belief seems correlated to a lower access to medical abortion in the general population. For example, the study by Pérez *et al*[16] showed that, in Spain, regions where a large part of the population is a practicing Catholic have a reduced access to gynecological services for abortion. Likewise, a study from Iran demonstrated an increased recourse to abortion in women with lower levels of Islamic religiosity and spirituality[22].

The fear of being judged unworthy by their religious community, as described in Poland by Zaręba *et al*[23], often leads women with strong religious beliefs to have abortion in health centers far from their hometown and avoid to confess it to their ministers. However, an organized religious activity seems to allow women to carry on with pregnancy after the discovery of fetal malformations having a better psychological outcome, compared to those who decided to have a TToP[24].

Gender and intimate partner violence

Taft *et al*[11] showed that women who have experienced or are currently experiencing any form of gender-based violence (psychological, physical, or sexual) are at higher risk of TToP or VToP. Women with a recent episode of non-domestic gender violence reported a significant risk of having an induced abortion (OR = 1.46 for adolescent women and 1.85 for adults).

Women who reported at least one experience of intimate partner violence (IPV) in their life have a 3 times higher risk of having a termination of pregnancy. The risk for an induced abortion seems higher in women with a recent episode of physical or sexual violence perpetrated by their partner.

Since the association between any form of gender violence, miscarriage, and preterm birth[11,25-27], it is mandatory for clinicians to investigate such aspects in patients asking for induced abortion.

PSYCHOPATHOLOGICAL DETERMINANTS OF TTOP

Several studies explored possible adverse outcomes of abortion on women's mental health, but, astonishingly, pre-existing mental health problems are often underestimated or neglected.

To evaluate the psychopathological determinants of choosing a termination of pregnancy is fundamental from an epidemiological and health economic points of view. Furthermore, the presence of pre-existing mental health issues could affect post-abortion mental health outcomes of those women[28-30].

There are already proofs that women who have had a TToP or a VToP may have higher level of psychopathology before abortion compared to other women who have never undergone one. Women who have a termination of pregnancy showed higher incidence rates of appointments with a psychiatrist or their general practitioner for mental issues, before and after abortion, than women who gave birth[31,32]. Another research[33] found that among women with psychiatric disorders and abortion, the majority of mental disorders occurred before ToP rather than after.

Termination of pregnancy in the female psychiatric population

van Ditzhuijzen *et al*[34] showed that the prevalence of axis I mental disorders was significantly higher in women who had a TToP or VToP (68.3%) compared to those who had not (42.2%). Compared to women who gave birth, those with an abortion (both VToP and TToP) have, after controlling for demographic factors, a 3 times higher risk of psychiatric history for any mental disorder[34]. Furthermore, women who have a termination of pregnancy are more likely to have previous psychiatric history than the controls. Authors[34] suggest two possible explanations: (1) An increased number of unwanted pregnancies in women with a history of mental disorders compared to healthy controls. This population may be more prone to other risky behaviors, such as unsatisfactory relationships, misusing of contraceptive devices, and substance abuse; and (2) A more frequent desire for TToP and VToP in women with psychiatric disorders. That wish could be mediated by factors related to their mental disorders and personality traits, such as low self-esteem, a pessimistic view abouttheir children life or doubts about their parenting skills, antisocial behavior, aggression, delinquency, or criminal behavior. Women with mental health issues could show a higher frequency of socio-cultural and economic factors related to the choice of having an induced

abortion, such as a low income or indigence.

Termination of pregnancy in women with anxiety disorders

According to several studies[33,34] women who have an abortion more frequently show a previous history of any anxiety disorder than women who give birth.

Analyzing different anxiety disorders, women who have a termination of pregnancy report a double history of panic disorder (OR = 2.06), social phobia (OR = 1.94), or specific phobia (OR = 2.30) compared to women who decide to give birth[34]. They also show a 1.5-1.9 times higher risk for agoraphobia and generalized anxiety disorder [33,34].

Several authors[33,35] attributed the correlation between anxiety disorders and increased use of termination of pregnancy to women's fear of gestation and childbirth (tocophobia), an aspect that has been described in women affected by anxiety, mood, and eating disorders.

According to Hofberg and Ward[35], although pregnancy is a normal and often desired condition, women may experience anxiety about physical and psychological consequences of pregnancy, sometimes with pathological connotations. Primary tocophobia[35], *i.e.*, not due to a previous negative gestational episode, appears to be due to 3 factors: (1) Social culture: It seems that the fear of gestation and childbirth can have an intergenerational transmission and, often, women's attitude towards pregnancy is strongly conditioned by the experiences reported by their mothers and grandmothers; (2) Pre-gestational anxiety disorders; and (3) Previous trauma: A history of childhood sexual abuse appears associated with aversion to gynecological examinations and obstetric care. Besides, the trauma of vaginal delivery (or even just contemplating it) can potentially cause the re-emergence of stressful emotions in women who have experienced a previous sexual abuse.

Termination of pregnancy in women with affective disorders

Mota *et al*[33] and van Ditzhuijzen *et al*[34] showed that women who have a termination of pregnancy show a 2 times higher risk of having a previous history of any mood disorder compared to those who give birth. In particular, those authors described a significantly increased history of major depression (OR = 1.51), dysthymia (OR = 1.79), and bipolar I disorder (OR = 2.8).

Furthermore, women with mood disorders who have abortion had more frequently a previous history of suicidal ideation (OR = 1.59) and attempted suicide (OR = 1.51) [34]. According to Mota *et al*[33], that evidence underlines that women with more severe forms of mood disorder are also those with the highest motivation to terminate pregnancy, probably because they feel incompetence towards motherhood duties. Several studies[36-38] highlighted more induced abortion in women with major depression and bipolar disorder under medications compared with women with the same disorder but drug-free when they have conceinved. The greater access to TToP could be explained by the concern of teratogenic damage due to psychotropic drugs.

The request for abortion in women with affective disorders is higher, especially in those taking fluoxetine and mood stabilizers (especially sodium valproate). Concerns are linked to the evidence of increased risk of fetal malformations and obstetric complications in women who take those medications during pregnancy, but clinical experience with women who are affected by epilepsy suggests that these consequences are rare and manageable with adequate antenatal planning[39,40].

It is crucial to understand the reasons that push women to ask for abortion, to provide them information on the real teratogenic risk of their therapy or to suggest alternative strategies to abortion, such as a switch tosafer drugs and careful antenatal care with ultrasound monitoring.

Termination of pregnancy in women with borderline personality disorders

Emotional and behavioral dysregulation experienced by patients with borderline personality disorders (BPD) may expose them at increased risk of unwanted pregnancy, compared to women without those symptoms[41]. Several studies[41,42] suggest that they may have earlier and unprotected intercourses than healthy women or women with different mental illnesses, due to their personality traits such as unstable attachment, impulsive behaviors, and compromised decision-making processes.

Furthermore, women with BPD show a greater predisposition to sexually transmitted infections (STDs) and associated consequences, such as pelvic inflammatory disease and infertility[41]. Other factors that can contribute to increas the risk of unwanted pregnancies and termination of pregnancy in those women are the higher prevalence of sexual abuse and comorbidity with substance use disorder (SUDs).

De Genna *et al*[42] found that the severity of BPD symptoms is directly correlated with the risk of having an unwanted pregnancy in adolescence, even controlling for socio-cultural determinants; in fact, in their sample, up to 18% of women affected by BPD becomes pregnant by the age of 16.

The effect of BPD severity on unwanted pregnancies and termination of pregnancy appears to vary depending on comorbidity with SUDs: women with severe symptoms but without a history of SUDs have more unwanted pregnancies with full-term births, while women who SUD have more induced abortion.

According to these authors, the risk of miscarriages, VToP and TToP in women with BPD would not be correlated with the severity of personality symptoms but, instead, it would be linked to demographic variables, such as low socioeconomic status, a young age when conceive, belonging to ethnic minorities or prostitution[42].

Termination of pregnancy in women with post-traumatic stress disorder

The relationship between termination of pregnancy and post-traumatic stress disorder (PTSD) seems bimodal. Even if PTSD has been widely analyzed as a possible consequence of the termination of pregnancy (see paragraph 4), it may also be a prior event and, accordingly, be a central determinant in the choice of having an abortion, especially in case of rape, IPV and separation of the couple.

Lundell *et al*[43] found that the prevalence of a previous traumatic event in the female population requiring termination of pregnancy was 43%: severe physical threats, severe psychological trauma and severe physical injury were the most reported traumatic experiences, while 12% of their sample experienced sexual assault or burglary.

Steinberg *et al*[44] showed a high frequency of childhood adversities or traumatic experiences with the current partner in a United States female population with medically assisted abortion. Authors reported that: (1) 50% of the sample claimed they suffered any childhood psychological abuse, 31.7% any childhood physical abuse, and 13% any childhood sexual abuse; (2) 25% of the sample reported episodes of domestic gender violence in the original family unit; (3) 34.6% of the sample declared they suffered any verbal violence, 7.4% any physical violence, and 4.8% any sexual violence by the current partner; and (4) 11.9% of the sample said they had been coerced into pregnancy and 7.4% had reported sabotage of their contraception devices by their current partner.

In a study by Mota *et al*[33] the prevalence of previous or current PTSD in women who had a termination of pregnancy was significantly increased compared to women who decided to give birth (OR = 1.91).

On the contrary, Wallin Lundell *et al*[43] showed a prevalence of PTSD in the female population requiring medically-assisted abortion around 7% and this value was not statistically different from that found in the general population. Although that finding, the authors described post-traumatic stress symptoms (PTSS) in 23% of women requesting a termination of pregnancy: It is possible that women with PTSS might be as susceptible as those with PTSD to traumatic consequences after an abortion and deserve approriate treatment[43].

In general, these findings support the importance of investigating the presence of previous traumatic events and previous or current post-traumatic stress symptoms in women who have an induced abortion, also to limit the onset or the worsening of PTSD after ToP.

Termination of pregnancy in women with psychotic disorders

Deinstitutionalization and second-generation antipsychotics, with fewer endocrine side effects (*e.g.*, hyperprolactinemia and amenorrhea), allowed women with schizophrenia spectrum disorders to be more sexually active, with a subsequent increase of pregnancies in this population. However, research focusing on the reproductive health of women with schizophrenia is sparse, and many studies are limited by small sample sizes[45]. Overall, women with psychotic disorders are more likely to have worse family planning knowledge than healthy women as personal relationships is one of the treatment areas with the most unmet needs[46].

Women with schizophrenia have more sexual partners in their lives, more rarely use contraception , and, consequently, have a higher risk of unwanted pregnancies and induced abortion than the general female population[46].

Simoila *et al*[45], with a 15-year follow-up on the reproductive health of women with psychotic disorders in Finland, found that 30.4% of women with schizophrenia and 29.9% of women with schizoaffective disorder had at least one termination of pregnancy (VToP or TToP) during the study period.

Patients with psychotic disorders showed significantly fewer births than healthy controls (0.65 birth per woman in the study group *vs* 1.72 births per woman in the control group): Up to 50% of affected women did not give birth in the study period, against 12% of healthy women.

According to these evidence, some of the reasons that led women with psychotic disorders to ask for abortion were younger age at conception and a lower chance of having a permanent partner at the time of the termination of pregnancy.

Examining the specific reasons behind the choice of termination of pregnancy, Simoila *et al*[45] found that: (1) VToP upon social indications (*e.g.*, low socioeconomic status) was the most common, both in women with psychotic disorders and in the general female population, involving up to 94% of women in both groups; (2) TToP for maternal health problems was significantly more common among women with schizophrenia and schizoaffective disorder than in healthy controls (2.1% *vs* 0.4%), maybe for medical conditions related to the disease or antipsychotics intake. Conversely, TToP for fetus health issues was significantly more common among controls than patients (3.1% *vs* 1.3%). That finding is somewhat unexpected since maternal schizophrenia seems related to fetal abnormalities, such as low birth weight and cardiac malformations, probably due to a linkage disequilibrium in genes related to heart and brain development[46]. The authors question this finding is related to pharmacotherapy efficacy in reducing fetal abnormalities or to the younger age of pregnant women with psychotic disorders[45]; and (3) No significant differences were found in the frequency of termination of pregnancy for ethical indication (*e.g.*, rape, IPV) between women with psychotic disorders and the general population. This reason was rare in both groups and that result was also unexpected because several studies[47,48] reported that women with schizophrenia experience higher rates of sexual abuse and gender-based violence.

Termination of pregnancy in women with SUDs

Women who have abortion are twice likely to have a current substance use disorder (OR = 2.16) than women who give birth. In particular, they show a 2 times higher risk of reporting a history of alcohol or drug abuse (OR = 2.29), and 4-5 times of alcohol (OR = 4.21) or drug addiction (OR = 4.96)[34]. According to van Ditzhuijzen *et al*[34], women with SUDs are more vulnerable to unplanned pregnancy and induced abortion than the general population due to risky sexual behaviors, such as poor use of condoms or other types of contraceptives and a large number of sexual partners. The risk of abortion is even higher among injecting drug users due to worse health conditions and clinical comorbidities, such as hepatitis C, HIV, and other physical disorders that can force that woman to choose for the termination of pregnancy. Women with endovenous drug use may be more vulnerable to indigence and discrimination, socio-economic factors that are linked to termination of pregnancy[34].

Furthermore, Diehl *et al*[49] demonstrated that the risk of TToP and VToP is increased in women who smoke tobacco (OR = 1.6) and in women with alcohol dependence (OR = 2.4), with a positive correlation between the severity of addiction (assessed with different screening tests for drug, alcohol and tobacco addiction) and the risk of medically assisted abortion.

In all the studies[34,49-51] that evaluated the relationship between SUDs and induced abortion, the most used substances were, in order of frequency, alcohol and tobacco, cannabis, opioids, cocaine, and, to a lesser extent, stimulants such as amphetamines.

The women's fear of gestational and fetal consequences due to drugs (*e.g.*, intrauterine growth restriction, higher risk of premature birth, miscarriages, and fetal abnormalities) can play a role in women's choice of termination of pregnancy. In fact, according to some authors[50,51], the recent policies of complete abstinence from drugs during pregnancy could lead to guilt feelings in women who used them during early gestation, that may lead them to decide to terminate the pregnancy even without evidence of any gestational or fetal consequence.

However, Roberts *et al*[51] showed that less than 5% of women who used alcohol, smoking, or other drugs in the first trimester of pregnancy considered substance use as the central determinant for VToP or TToP. Moderate alcohol consumption was not significantly associated with the decision to terminate the pregnancy, while 84% of women who recognized alcohol consumption as their reason to have an induced abortion were binge drinkers or patients who were previously diagnosed with SUD or alcohol-related physical problems.

It is therefore important to highlight that substance use, which is modest in the general healthy population, does not appear to be a determining factor in the choice of ToP in the majority of people, but is an important element in the decision-making

process of women with a SUD or with physical problems related to addiction[34,51].

Termination of pregnancy in women with childhood psychiatric disorders

A predictive association between a woman's childhood and adolescent mental health and her future choice to terminate a pregnancy,for social reasons and for maternal determinants, has been supposed.

A Finnish study[52] showed that there is an association between childhood and adolescent mental health and the risk of having a ToP when young (in women under 20 years) or having repeated induced abortions. Those evidence highlight the importance of implementing sex education for adolescents suffering from psychiatric and neuropsychiatric diseases, to limit their obstetric and reproductive issues.

van Ditzhuijzen *et al*[34] found that women whit a history of any childhood impulse-control disorder show a higher rate of induced abortion than healthy women (OR = 4.35). In particular, the most common childhood impulse-control disorders in women who had TToP and VToP were respectively conduct disorder (OR = 1.72)[33], oppositional defiant disorder (OR = 1.67-2.99)[33,34], antisocial personality disorder (OR = 3.87) and conduct disorder (OR = 6.97)[34]. Moreover, women with a diagnosis of attention deficit hyperactivity disorder (ADHD) in childhood (especially patients with greater impulsiveness) showed a 3 times higher risk to have an induced abortion [34].

Several studies conducted in Northern Europe[52,53] support the existence of a link between a history of childhood conduct disorder in women and medically assisted abortion. According to those authors, girls with conduct disorders can be involved in risky impulsive sexual behaviors with a higher risk of unwanted pregnancy, sexually transmitted diseases, and adolescent sexual abuse. In particular, Lehti *et al*[52] observed that a poor school performance during primary and secondary school can be considered as an independent predictor of subsequent terminations of pregnancy in that population, according to the fact that a low level of education is an important determinant of TToP and VToP (as underlined in paragraph 2 "Demographic and reproductive determinants of termination of pregnancy").

Termination of pregnancy in women with eating disorders

Several studies[54-56] documented a correlation between a history of eating disorder and various gynecological comorbidities, such as impaired menstrual function, infertility, increased risk of unwanted pregnancy, gestational complications (*e.g.*, low birth weight, preterm birth, pregnancy bleeding, gestational diabetes, hyperemesis gravidarum) and a higher risk of oophorectomy and hysterectomy.

Bulik *et al*[55] showed that women with anorexia nervosa (AN) have a higher risk of teenage pregnancy and unwanted pregnancy (OR = 2.11) than women without any eating disorders, with more than 50% of subjects reporting unscheduled conception and a history of prior VToP. The risk of unwanted pregnancy and VToP seems higher in this population with a history of amenorrhea or oligomenorrhea in the year before conception, suggesting that menstrual irregularities may reduce patients' adherence to contraceptive use. Bulik *et al*[55] showed that, despite menstrual irregularities, women with AN and bulimia nervosa (BN) can still conceive and their gynecological comorbidities (infertility, amenorrhea) can give them a false sense of security in unprotected sexual intercourse. According to authors, a better sexual education for patients with eating disorders could make them more aware of the risk of pregnancy even during menstrual irregularities and thus reduce the use of medically assisted abortion.

O'Brien *et al*[54] noted an increased risk of miscarriage (OR = 1.19), VToP, and TToP (OR = 1.25) in patients with AN and BN, especially in women who had a later onset of the eating disorder (18-22 years old).

Similarly, Linna *et al*[56] showed a higher proportion of VToP and TToP in women with classical BN (OR = 1.85) and atypical BN (OR = 1.92) and in women with AN (approaching statistical significance in the latter, with OR = 1.62, P = 0.06). Women with binge-eating disorder (BED) did not show an increased risk of termination of pregnancy.

Termination of pregnancy in women with paraphilic disorders and sexually compulsive/behaviors

Due to cultural background and social stigma, women may have difficulties in identifying themselves as affected by compulsive sexual behaviors or sexual addiction. Furthermore, some people show a sexual pattern of "binge-starvation", characterized by the alternation of periods of extensive sexual activity ("sexual binging") and periods

of complete abstinence ("sexual anorexia")[57,58]. In the context of paraphilias and sexual compulsions, women are more inclined to sexual submission or victimization compared to their male counterparts, although sexual dominance behaviors in women are also increasing[58].

Fear of rejection and feelings of shame, associated with compulsive or addictive sexual behavior or uncontrolled paraphilias, prevent women from developing intimate relationships: in fact, it is common for women with dysfunctional sexual behavior to avoid affective attachment with their partners and more often build unstable families [57,58]. All these elements can contribute to the choice of women with paraphilic disorders and sexually addictive/compulsive behaviors to terminate a pregnancy.

Roller[57] investigated the consequences of these disorders on the reproductive health of women, such as: (1) A higher risk of sexually transmitted infections, cervical and vaginal cancer (linked to chronic HPV infection), pelvic inflammatory disease, infertility, and ectopic pregnancies; (2) A higher rate of miscarriage, due to major obstetric complications, but also to gynecological trauma determined by violent sexual practices, sometimes practiced even during gestation; and (3) A higher frequency of unwanted pregnancy (40%-70%), VToP and TToP (36%), and feelings of discomfort and inadequacy during gestation and motherhood (60%).

PSYCHOPATHOLOGICAL CONSEQUENCES OF TTOP

A medically induced abortion can have important consequences on the mental and reproductive health of women because termination of pregnancy is a traumatic event for parents.

Pregnant woman and the baby's father experience induced abortion differently, and woman reaction might also be influenced by her will to give birth and by the moment of the pregancy when she has abortion.

Fergusson *et al*[59] showed that TToP has a greater traumatic burden and psychiatric morbidity compared to VToP or miscarriage, that normally occur at an earlier stage of the pregnancy.

According to authors[59-61], this finding could be explained with different reasons: (1) Taking place in the second trimester, TToP is performed with a surgical procedure, unlike the medical abortion for VToP or uncomplete miscarriages; (2) In case of TToP, parental desire for a child clashes with emerging medical issues and it is performed later during the gestation, when the couple gets already used to their parental role; (3) In the first trimester, women do not perceive fetal movements and the relationship with the baby is weaker than in later stages of gestation; and (4) After the TToP, parents can hold the child in their arms and can photograph him after the abortion procedure.

It is also important to highlight that TToP is performed with a therapeutic aim and it can also have positive outcomes, especially for those with high levels of distress due to the diagnosis of fetal malformation. It is always important to evaluate the context and the factors that lead a woman to ask for TToP to predict different outcomes she might experience.

Positive mental consequences of TToP

Despite several studies concerning the negative consequences of TToP, it is important to underline that TToP is a medical act performed with a therapeutic purpose.

In this regard, several authors measured a significant improvement after TToP of pre-abortion psychopathological distress , especially mood and anxiety symptoms[60, 62-64].

Interestingly, women's mood seems to improve significantly in the long-term after TToP: Major *et al*[65], measured depressive symptoms with the BDI in different moments before and after TToP and discovered that, immediately after TToP, women's average score was under the cut off for mild depression and their mood significantly improved 3 wk later. A similar positive pattern in anxiety symptoms after TToP has been shown by Cohen and Roth[64].

Depression and anxiety symptoms after TToP

Usually, after TToP women experienced a significant improvement in their mood compared to the period before the induced abortion, but in a minority of cases, women showed long-term depressive and anxiety symptoms and sense of guilt after the procedure[62,66,67].

Zolese and Blacker[68] found that the most common long-term consequences of TToP are depression and anxiety disorders, while psychosis is uncommon. These disorders cronicize in around 10% of women.

Di Febo *et al*[62] show that poor partner support and relational problems related to abortion are the most important risk factors connected with significantly worse mood outcomes after TToP. An increased risk of long-term depression and anxiety disorders was also observed in women with a previous psychiatric history, in young and pluriparous women with poor social support, and in those belonging to social or religious groups that do not accept abortion[66,67].

Furthermore, different authors[12,69] showed that women are more likely to be depressed before abortion than after it; as previously underlined, depression after TToP could highlight a pre-existing mood disorder.

These findings support the importance of the assessment of socio-cultural and psychopathological determinants in all women who have a TToP to predict possible depressive or anxiety consequences.

Post-abortive mania

Several reproductive events (menarche, menstruation, childbirth) are associated with increased mood alterations in women with bipolar disorder; however, little is known about the impact of termination of pregnancy on the course of bipolar disorder[70].

Mahe *et al*[70] described the case of a woman with a history of 5 full-term pregnancies and 2 abortions (1 VToP and 1 TToP) in which each reproductive event was followed by an episode of psychotic mania. There are currently no studies that systematically examined the relationship between abortion and mania among women with bipolar disorder, probably because post-abortion mania is much less common than post-abortion psychosis[70]. A Danish study reported a similar risk of re-hospitalization in women with bipolar disorder before and after medically induced abortion, a possible sign that this reproductive event would not be associated with a clinical worsening of the disease[31].

Mahe *et al*[70] described several clinical cases of post-abortion mania and, according to them, the post-abortion period could be at increased risk of converting bipolar II disorder to bipolar I, due to a worsening of manic symptoms in women who have TToP or VToP. Furthermore, the termination of pregnancy could constitute a trigger for manic episodes in healthy women with a predisposition for affective disorders[70].

Post-abortive psychosis

Brockington and Guedeney[71] reported at least 30 cases of psychotic episodes following abortion, including one historical case described by Esquirol in 1819. The episodes occurred in women with schizophrenia as well as in women who had never previously suffered from a psychotic disorder.

Post-abortion psychosis seems very rare: Brewer[72] found a 0.3/1000 hospitalization rate of post-abortion psychosis compared to 1.7/1000 post-partum psychosis after delivery.

The clinical presentation of post-abortion psychosis is similar to puerperal psychosis and the onset typically occurs within 2 wk after TToP. Individual predisposition and estrogenic fluctuations are supposed as the major causal factors in post-abortion psychosis and puerperal psychosis[73]. Guillaume *et al*[74] suggest that the risk of psychosis may be proportional to the degree of estradiol levels drop associated with the end of pregnancy (*e.g.*, following delivery, miscarriage, and induced abortion).

PTSS and PTSD after TToP

Retrospective studies[75,76] showed that TToP is a traumatic event that leads to severe post-traumatic stress responses and whose distress may be evident years later. A prospective study[76] showed that TToP for fetal abnormalities is associated with an increased risk of PTSD compared to VToP.

However, research regarding the relationship between TToP and PTSD development had controversial results. Geerinck-Vercammen and Kanhai[75] studied 89 couples at 6 wk and 6 mo after TToP and they concluded that PTSS were experienced at the time of abortion and in the following weeks, but they disappeared after 6 mo, but, this survey was based only on a semi-structured interview. By contrast, in a Dutch sample[76] women showed PTSS and depression even years after a TToP for fetal malformations.

Kersting *et al*[77] examined a sample of women who have had TToP, with different psychometric scales (MADRS, BDI, IES-R, SKID) over 14 wk and found that, despite the frequent development of intense PTSS in women 2 wk after the TToP (64.5% of the

sample), at 14 wk the prevalence of PTSD was much lower (22%). Accordingly, although post-traumatic symptoms can be very common in the short-term after TToP, only about 20% of women develop long-term PTSD.

SUDs after TToP

A connection between VToP and increased use of alcohol, tobacco, and illicit drugs is well described[78], but this relationship is rarely investigated in case of TToP.

Drower and Nash[79,80], in a 18 mo follow-up, showed a 2 times higher risk of alcohol, tobacco, or illicit drug abuse in women who had a TToP. In fact, women who have TToP are 1.5 times more likely to abuse tranquilizers compared to women who gave birth[79,80].

Determinants of psychopathological outcomes of TToP

Women who have an induced abortion (TToP and VToP), may have several factors linked to a higher risk of psychological distress in response[81].

Medical or genetic indication: Several studies[82,83] showed that the use of TToP for maternal or fetal health reasons (*e.g.*, malformations or genetic issues) increases the risk of negative psychological reactions compared toVToP performed on ethical or social indications (*e.g.*, rape, incest, low socio-economic status).

Socio-cultural and demographic factors: Women at greatest risk of negative psychological consequences aresingle, nulliparous, immigrant, or belonging to cultural minorities, young (< 30 years, especially adolescents)[81]. The relationship between strong religious feelings and psychological consequences is contradictory: Romans-Clarkson[81] pointed out that religious belief is not associated with increased guilt after TToP, but Payne *et al*[84] claimed that a negative religious or cultural attitude towards abortion is one of the major risk factors for adverse psychological outcomes.

Coercion of the procedure by partner or parents: All the legislations emphasize that the choice of TToP/VToP is personal[2], but women can be pushed to make a decision against their desire for their pregnancy, with an increasedrisk of negative psychological outcomes[81]. Women who have independently chosen for a termination of pregnancy show lower risk of negative psychological effects, even if adolescent[85].

Psychopathology and psychiatric history before the procedure: Women who experienced greater psychological distress before the abortion were more likely to have low self-esteem and a high sense of alienation after the procedure[86]. Moreover, women with an internal locus of control and high levels of resilience showed positive outcomes after TToP/VToP[87].

Presence of emotional support: The extent of emotional support a woman perceives during abortion is positively correlated with a good psychological response[81]. On the other hand, Major *et al*[65] found that if the partner is present during abortion, there is a higher risk of depressive symptoms and sense of guilt. Similarly, Robbins[88] found that single women who maintained a strong relationship with the father of the unborn, after abortion were much more at risk of negative psychopathological outcomes. Instead, Romans-Clarkson[81] showed a higher risk of a negative psychological outcome in women with absent or weak family bonds, fewer friends and excessive work pace, partner abandonment, and absence of family support for children care.

Presence of conscious fantasies about the fetus: the intensity of thoughts about the baby seems directly correlated with the risk of negative psychological consequences [81].

Illegal abortion: Diggory[89] suggested that illegal abortion is associated with depressive reactions and feelings of guilt after TToP and VToP.

Absence of contraception: Important sense of guilt and depressive reactions is described in women who do not use contraception[81]. Some authors highlighted the importance of providing adequate contraception education after an induced abortion, both to limit the future recourse to the procedure and their self-blame reactions[81].

CONCLUSION

Several studies evaluated which decisional factors (socio-demographic, reproductive,

psychopathological determinants, and fetal abnormalities) may lead women to induced abortion, but many studies do not discriminate between therapeutic and voluntary ToP, thus representing a possible bias in discriminating decisional determinants of TToP.

Women who have a TToP are usually over 35 years old[3,9], more often divorced or unmarried[3,9], with a high educational level[3,9], but low socio-economic status and a low monthly income. They usually have more children[3], live in large urban areas[11] and belong to ethnic minorities or are immigrants[17], do not have strong religious beliefs[16], and more often report any form of gender-based violence[27].

Women with TToP and VToP show common reasons for their decision, mostly linked to personal and social difficulties that may prevent adequate child care. That evidence stresses the importance of social assistance to support women with those factors.

Women who choose TToP are more commonly affected by a previous mental disorder[28,31,33], that probably influences their mental outcomes afterward.

Results by van Ditzhuijzen *et al*[34] and Mota *et al*[33] showed higher prevalence of any axis I psychiatric disorder in those women, with increased rates of anxiety and mood disorders[33,34], SUDs[34], impulse control disorders[34], ADHD[34], PTSD[33,43], psychotic disorders[45], eating disorders[54], sexually compulsive/addictive behaviors and paraphilias[57].

Interestingly, current knowledge does not discriminate any specific major psychiatric disorder as more relevant in the decision to have abortion.

The correlation between a higher rate of TToP and personality disorders is less investigated and data are limited to women with antisocial personality disorder[34] and borderline personality disorder (BPD). De Genna *et al*[42] explained the link between BPD and TToP with worse reproductive wellness, a huger number of unplanned and early pregnancies (< 25 years), sexual-transmitted infections, unsafe sexual intercourse, and history of childhood trauma and sexual abuse. Women with some personality disorders are more keen to unwanted pregnancies and those affected by such disorders are rising more and more in the general and clinical population. Accordingly, an in depth analysis in those populations should be encouraged to identify specificities and offer better support.

Interestingly, TToP produces both positive and negative psychopathological effects in women.

Evidence[60,62,64] showed that women with a TToP experience a significant improvement in the psychological distress, mood, and anxiety symptoms they felt before. In fact, even if TToP involves strong negative feelings like guilt and sadness, the difficulties of raising a child with illness seems even worse for some women. Those women deserve support and respect in a very delicate moment that implicates ambivalent feelings and sufferance.

Furthermore, Zolese and Blacker[68] demonstrated that only a minority (10%) of women have psychological or psychiatric disorders after a TToP and several authors [67,68] found that negative psychic outcomes after TToP are more frequent in women with previous psychiatric history (*e.g.*, depression, anxiety disorders, mania, psychosis, and SUDs)[33,70,79]. Therefore, in most cases psychiatric consequences of induced abortion are an exacerbation of pre-existing conditions and they are not an onset of psychopathology.

Nevertheless, concerning outcomes of TTOP are demonstrated by a higher rate of post-traumatic symptoms, especially in the short-term, with a persistent post-traumatic stress disorder in about 22% of the women[77].

In conclusion, we emphasize the importance of providing psychological and psychiatric support to all women who want a TToP, to predict and limit adverse outcomes on their mental and reproductive health. Moreover, further studies are needed to assess the mental history of the male partners and their possible outcomes after a TToP.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 954-980

DOI: 10.5498/wjp.v11.i11.954

ISSN 2220-3206 (online)

REVIEW

G-protein coupled receptors and synaptic plasticity in sleep deprivation

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Author contributions: Parmar S, Tadavarty R and Sastry BR contributed equally to the outline of this review; Parmar S performed 85% of the writing work, and Tadavarty R performed 15%; Illustrations were done by Parmar S; Suggestions and corrections were contributed by Sastry BR; All authors have read and approved the manuscript.

Conflict-of-interest statement: Authors have nothing to disclose.

Supported by Canadian Institutes of Health Research Grant, No. TGS-109219; and 4-Year Fellowship from the University of British Columbia.

Country/Territory of origin: Canada

Specialty type: Neurosciences

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C

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Abstract

Insufficient sleep has been correlated to many physiological and psychoneurological disorders. Over the years, our understanding of the state of sleep has transcended from an inactive period of rest to a more active state involving important cellular and molecular processes. In addition, during sleep, electrophysiological changes also occur in pathways in specific regions of the mammalian central nervous system (CNS). Activity mediated synaptic plasticity in the CNS can lead to long-term and sometimes permanent strengthening and/or weakening synaptic strength affecting neuronal network behaviour. Memory consolidation and learning that take place during sleep cycles, can be affected by changes in synaptic plasticity during sleep disturbances. G-protein coupled receptors (GPCRs), with their versatile structural and functional attributes, can regulate synaptic plasticity in CNS and hence, may be potentially affected in sleep deprived conditions. In this review, we aim to discuss important functional changes that can take place in the CNS during sleep and sleep deprivation and how changes in GPCRs can lead to potential problems with therapeutics with pharmacological interventions.

Key Words: G-protein coupled receptors; Metabotropic glutamate receptors; Gamma-amino butyric acid-B receptor; Synaptic plasticity; Sleep deprivation; Memory consolidation

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Core Tip: Sleep hygiene is thought to be necessary for memory consolidation and learning while sleep disturbances can alter both synaptic plasticity and memory consolidation. Recent findings indicate that the expression of G-protein coupled receptors

Grade D (Fair): 0
Grade E (Poor): 0

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Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: May 13, 2021
Revised: June 5, 2021
Accepted: September 19, 2021
Article in press: September 19, 2021
Published online: November 19, 2021

P-Reviewer: Jarmasz JS
S-Editor: Liu M
L-Editor: A
P-Editor: Yu HG

(GPCRs) like metabotropic glutamate receptors, gamma-amino butyric acid-B receptors and serotonin (5-hydroxytryptamine) receptors as well as synaptic plasticity are altered following a short episode of sleep deprivation. GPCRs are involved in a variety of central nervous system functions and are targets for therapeutic agents in psychiatry and other neurological disorders. Therefore, a deeper understanding of these receptors in association with the state of sleep and its related functions and disorders is needed.

Citation: Parmar S, Tadavarty R, Sastry BR. G-protein coupled receptors and synaptic plasticity in sleep deprivation. *World J Psychiatr* 2021; 11(11): 954-980
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/954.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.954

INTRODUCTION

Sleep is one of the fundamental needs of most conscious living beings. Earlier sleep was more analogous to just the idea of resting and having our mind and body recharge for the activities in our consecutive state of wakefulness. We have moved far along from this initial notion as we now know that even in the state of rest, our body is constantly working right from the molecular to the more visible physiological and psychological levels. The implications associated with sleep deprivation manifest themselves both behaviourally as well as physiologically. In a way, both these implications are correlated considering external stimuli enables an animal to act in a certain way depending on what kind of signals the brain has processed. The processing of such signals is mediated by cellular components like genes and proteins. In different neurological disorders like depression, loss of memory, psychosis, hallucination, anxiety, *etc*., certain biomolecules are differentially affected. Synaptic plasticity which is thought to be a cellular correlate involved in memory consolidation and learning, is also affected following sleep deprivation.

In this review, therefore, we aim to understand and highlight the fundamental properties of sleep and sleep deprivation by keeping memory consolidation and synaptic plasticity as representative functions which get affected by the different states of sleep. In addition, any changes in G-protein coupled receptors (GPCRs) caused by sleep disturbance are emphasised.

THE DYNAMIC STATE OF SLEEP

Sleep and its significance

Sleep is indispensable for most animals. Extensive studies in this area have now led us to believe that sleep is not a static phenomenon but it is heterogenous and dynamic even if its physical nature appears completely passive. There are interconnections between the thalamus, cortex and hippocampus regions of the brain and this interplay of networks is known to be operated by stage specific oscillations that take place while we are asleep[1,2]. Aserinsky was one of the first researchers whose studies overcame the concept of the cerebral cortex being dormant in sleep and gravitated the scientific community towards the reality of the brain being in an active state even while we are asleep[3]. There are stages or periods in sleep which transition alternatively from an active period, which is manifested by rapid eye movements (REM) to an inactive or quiescent period, also known as the slow-wave sleep (SWS)[3]. The oscillation patterns in the brain fluctuate during these two stages of sleep with high frequency and low amplitude waves being a characteristic of the REM/Late-night paradoxical sleep and the SWS portraying the contrary wave pattern[2,3]. Advancement in this area has revealed many more biological functions like respiration, thermoregulation, *etc*., along with the neurobiological processes of learning and memory formation in association with the alternating stages of REM sleep and SWS[4].

Disturbances in regular sleep cycles were assessed through the monitoring of EEG patterns. Waves of low amplitude and high frequency, associated with wakefulness, also occur during REM sleep. Deprivation of sleep is usually followed by a compe-

nsatory increase in REM sleep (REM rebound). This increase is interpreted to indicate an attempt in re-establishment of homeostasis in learning and memory as well as emotional balancing[5]. Non-REM sleep is associated with high amplitude and low frequency delta waves (stages 3 and 4) along with stage 2 spindle activity[2,3]. Sleep deprivation increases the amplitude of the waves associated with spindle activity but reduces spindle density[6-9]. Upon chronic sleep restriction, the power density of theta wave frequency increases[10,11]. Therefore, lack of sleep seems to result in changes in REM as well as non-REM sleep.

The functional significance of sleep guides us towards the negative implications of sleep deprivation. A balanced and sufficient sleep cycle acts as one of the major factors that determine the quality of human life. There are a wide range of environmental, psychological and physiological factors that lead to sleep deprivation. Environmental changes have influenced many aspects of our day-to-day life and sleep disturbances can arise due to an increase in surrounding noise as well as fluctuations in light and temperature[12]. These factors add on to the list of causes that negatively burden the state of mind. Mental health also plays a crucial role in maintaining a regular sleep pattern since the prevalence of stress, anxiety, depression, *etc.*, affects regular sleep cycle which can translate into insomniac conditions. Psychosis disorders like schizophrenia or neurodegenerative diseases like Alzheimer's have often been associated with issues related to sleep deprivation like a reduced REM sleep cycle as well as a lowered sleep spindle activity[13,14]. Apart from mental disorders, pathophysiological illnesses (*e.g.*, cancer, diabetes, respiratory disorders *etc.*) also often result in sleep disturbances due to manifestations like pain or difficulty in breathing. Interestingly, lack of sleep can also increase the prevalence of such physiological disorders since an important function of sleep is the regulation of the immune system[15]. Modern lifestyle changes like uneven working hours, over consumption of caffeine along with an increase in screen-time exposure have potentially interluded the quality and quantity of sleep. Homeostasis of the normal biological circadian rhythm is required for better cognition and task performance. For example, studies have implicated that night shift-workers, especially in chronic situations, experience varying levels of cognitive impairment and task performance[16,17]. Drug abuse and alcohol consumption which can lead to substance use disorder have also been recognized as a growing cause of sleep disruption. For instance, alcohol consumption is indicated to suppress REM sleep which in turn causes impairment in performing procedural tasks [18]. Conversely, lack of sleep affects the activity balance of important neurotransmitters like dopamine (DA) in the brain and this has been indicated to increase vulnerability to the use of drugs[19]. The above mentioned negative influences of sleep deprivation are just few of the many but it helps in bringing the importance of sleep deprivation into perspective.

Without sufficient amount of sleep, the brain cannot adequately perform the processes that take place during the state of sleep. Sleep deprivation affects the ability to concentrate, intake information and mediate that information through neuronal signalling, learn as well as process memories for consolidation. Furthermore, it is affected by the signalling and expression profiles of many biological molecules including the GPCRs[20,21]. These functions are related to the different stages of sleep and hence there are stage specific implications of sleep deprivation. For example, lack of REM sleep has been directed towards to an impairment in the development and expression of emotional and spatial memories[22,23]. Additionally, disruption of SWS is suggested to reduce attention span, affect motor activity and task performance[24]. Since learning and task performance are dependent on the memory processing of various responsible stimuli, the concept of memory consolidation has been highlighted to understand the significance of sleep and its associated cellular machinery.

Sleep and memory consolidation

Memory is the ability of living beings to retain information that they have acquired through their various day to day experiences and activities. The brain consolidates memories in different stages starting first from acquiring the memory through learning experiences, encoding and then consolidating those memories to be recalled or retrieved upon stimulus[25]. Interestingly, even the processed memories can become transient overtime and a reconsolidation of those memories is required for which sleep is essential[26]. While we sleep, the brain is actively carrying out its functions and 'offline-reprocessing' of memories appears to be one of them[3]. The presence of the rapid and spontaneous oscillations in the cortical networks of the brain during wake and sleep periods have been known to get triggered upon sensory stimuli [27,28] which can get incorporated in the brain in form of a memory. This gradual incorporation of acquired memories into the different regions of the brain is more

crucial for long term memory than the short-term memory, which points towards a quicker mechanism of action[29,30]. REM sleep and SWS are generally associated with the consolidation of long-term implicit (non-declarative) and explicit (declarative) memories, respectively[31-33], both working in a double-step process. In support of the alternate nature of the REM sleep and the SWS, work done on the memory consolidation function of these stages has revealed that SWS also has its part to play in reactivation and redistribution of the spatio-temporal patterns of the neurons which are observed during the encoding stage of memory function when we are awake[31, 34-36]. When there is distraction or disruption of the periods immediately after the learning or teaching stimulus, the formation of memory is interrupted and consequently the task reperformance associated with that memory is affected[29,30]. Now, since memory is processed during the state of sleep, it appears that disruption of this state during sleep deprivation can also affect memory consolidation in the brain. For instance, there have been studies demonstrating how lack of sleep can cause weak recollection of visual stimuli or how motor skill learning improvements are dependent on a good night-time sleep[37-39].

The discussed oscillation and wave patterns during the state of sleep are at least partly a result of the electrical impulses that are transmitted between neurons *via* the synapses. This transmission modifies the synapses and hence synaptic plasticity is an important consideration while studying about the various functions of sleep including memory consolidation. To better understand this correlation, we will first discuss the regions and cells of the brain that are associated with sleep dependent functions and how these regions communicate *via* signal transmission.

The cortical hippocampal dialogue

As mentioned earlier, activities in the brain during the state of sleep are in conjunction with changes in the oscillation and wave-patterns in specific regions of the brain. These complex wave-sequences form a characteristic component of the neocortical and the thalamic system, which co-ordinate in order to exhibit the various functions of sleep, including memory consolidation. Although the mechanisms that are involved in the functions and regulation of memory consolidation are yet unclear, various cellular processes in brain regions have been studied as potential candidates. Amongst these, the hippocampus is one of the main centers for processing sleep dependent memories through neurons like granule cells and pyramidal cells[40]. The significance of the hippocampus and its sub-regions may be attributed to its function of independently giving the neuronal networks the ability to process multimodal information and building an integrated system that can represent the newly acquired information for its consequent storage in the higher centers of the brain in the form of 'memories'[41]. Inspired by this finding, a two-staged memory consolidation concept was put forward which essentially highlighted the events wherein there occurred a transmission of information between the hippocampus (short-term storage) and the neocortex (long-term storage) through the exploratory theta burst stimulations of the granule cells and sharp waves of the pyramidal cells[42]. While the hippocampus is concerned with high frequency oscillations and sharp wave ripples in the CA1 and CA3 regions, the neocortex shows slow oscillations and spindles during SWS[43]. During SWS, the signal from the hippocampus to the neocortex is transmitted through the CA1 neurons whereas during REM sleep the information enters the hippocampus from the neocortex through the CA3 neurons; thus, causing the CA1 neurons to hyperpolarize the CA3 neurons through the entorhinal cortex[43]. This rhythmic communication of oscillations gives rise to coupling as well as consistent spike timing relationship between the neocortex and the hippocampus which further strengthens the information processed for learning and memory consolidation[43-45].

As discussed above, there seems to be a pattern of relay of information that is associated with sleep dependent functions between the hippocampus and the neocortex. Since the relayed signals go through synapses, any plasticity at the junctions can significantly alter the above mentioned patterns. Therefore, in this review, a discussion on the phenomenon is made.

THE ROLE OF SYNAPTIC PLASTICITY IN SLEEP AND LEARNING

The active nature of brain during the state of sleep so far has been advocated by multiple studies on the specific regions of the brain which primarily show distinct wave patterns and relay information through signal transmission. Transcending from the Hebbian[46] theory, the strength of these signals has been associated with the

continuous firing of action potentials from a pre-synaptic neuron to a post-synaptic neuron. It has appeared that a signal gets stronger when it is repeatedly transmitted from one synapse to another and this is where the phenomenon of synaptic plasticity comes into play. When there is continuous firing of signals between neurons, there are changes that take place at the synapses of these cells, which means that the cellular components at these junctions also undergo changes and consequently affect the strength of the signal being transmitted. This concept can be appreciated by looking at instances wherein it appears that by repeatedly performing a task, we get better and better at it. In a similar way, a repeated stimulus to the brain results in repeated signal transmission from one neuron to another and this can have the potential to strengthen that signal[46]. This takes place through synaptic plasticity which entails molecular as well as electrophysiological changes at the synapses. The electrophysiological changes can be characterized by long term depression (LTD) and long term potentiation (LTP), each relating to the persistent weakening and strengthening of the synapses, respectively. Initial work done in this area revealed that at the excitatory synapses, there occurred a use-dependent and long term strengthening of the synapse upon high frequency stimulation of the pre-synaptic fibres in the hippocampus, which was termed as LTP[47]. Analogous to the Hebbian[48] findings, experimental data at cellular level has indicated that synaptic plasticity in the form of LTP in the hippocampus is input specific and can be associative in the sense that if activity in inputs coincides with a depolarization of the post-synaptic neuron, the active synapse gets strengthened[48-50]. The post-synaptic depolarization is thought to remove a Mg^{2+} block of the N-methyl-D-aspartate (NMDA) receptor coupled ionic channel allowing a Ca^{2+} influx which activates protein kinases that sets up the expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the dendritic spines at synapses leading to an increase in response to the released glutamate, the transmitter[51]. The post-synaptic depolarization is also suggested to facilitate the release of a retrograde messenger that causes an increase in glutamate transmitter release and, thus, an increase in synaptic transmission[49]. Upon stimulation of synapses at lower frequencies than those that induce LTP, the induction of LTD also involves an influx of Ca^{2+} ions, although the surge of Ca^{2+} ions is comparatively lower than that in case of LTP[52]. The difference in the level of Ca^{2+} influx results in activation of phosphatases that are responsive to lower concentration of Ca^{2+} ions. This subsequently leads to a dephosphorylation of AMPA receptors and a reduction in their activity which decreases the response to the released glutamate and causes an overall reduction in synaptic efficacy[53]. Therefore, the phosphorylation of AMPA receptor through kinases in LTP is counteracted by the phosphatases during LTD which leads to an interference and reversal of LTP. This interplay promotes modulation of synaptic plasticity which as explained in the section below, appears to be crucial for memory processing and learning. The comparative details of LTP/LTD associated molecular events are summarized in Table 1 and are also discussed further in subsequent sections of this review[54-66].

The process of learning and memory consolidation that takes place while we are asleep can also be attributed to further molecular changes that can take place following the synaptic strengthening. A disruption of these due to sleep deprivation can, thus, have a negative consequence.

LTP and LTD as cellular correlates for learning and memory formation

In spite of having a breakthrough discovery about LTP and LTD causing long-lasting modification in the synapses in the 1970s[47,67], the functional implications of LTD and LTP in learning and memory processing are still under a lot of conjecture. While the initial studies relied more on the active state of synapses through LTP as the focal model for learning, subsequent studies also implicated the role of LTD by highlighting the fact that a consequent increase and decrease in signal strength is what allows the phenomenon of synaptic plasticity to function without getting worn out[52,58,59,68]. For instance, Tsumoto[65]'s work highlights LTD in cerebral cortex being responsible in 'forgetting' certain memories in order to make place for the new ones. Looking back at Hebbian[46] and the follow-up findings, the role of synapses and the existence of synaptic plasticity as cellular correlates of learning and memory consolidation become apparent. As discussed in the previous sections, learning and memory consolidation are a result of collective cellular communications through the processing of the learning stimuli. The cortical-hippocampal dialogue is thought to drive these learning stimuli forward in the brain to encode, process and store the information acquired through those stimuli. Several lines of studies demonstrate the correlation of memory acquisition with the processing of spatial learning to LTP and LTD[65,66,69]. Furthermore, exploratory behaviours and learning are known to promote information

Table 1 Comparative features of long term potentiation and long term depression and their implications in sleep and associated functions

	Prominent brain regions	Receptors involved	Induction	Maintenance	Association with sleep	Functional significance
LTP: Strengthening of synaptic transmission due to a transient high frequency stimulation of the synapses	Cerebellum, hippocampus, cerebral cortex	Ionotropic: NMDARs, AMPARs	Requires activation of both pre- and post-synaptic neurons at the same time for glutamate to fully activate the NMDA receptors [51].	Secondary activation of receptors like AMPARs by glutamate needed for maintenance of LTP [51].	Active nature of LTP likely associated with active state of sleep.	Enhances synaptic response as well as neuronal excitability.
		Metabotropic: Group I mGluRs	Ionotropic induction requires activation of NMDARs by glutamate released from pre-synaptic neurons for higher Ca^{2+} influx in the post-synaptic neuron [51].	Requires activation of intermediate protein kinases like CaMKIV, protein kinase M-ζ, PKA etc. by high Ca^{2+} concentration to release membrane obscured AMPARs [56].	More commonly linked with REM sleep associated cellular and molecular modulation of synaptic plasticity [57].	Involved in memory consolidation and learning: Strengthened synapses promote long-term memory storage[58]; Promotes associative and spatial learning[59]; Involved in motor learning and task reperformance [60,61].
			Metabotropic induction works *via* an increase in intracellular Ca^{2+} release through mGluR activated phospholipase C and synthesis of secondary messengers IP3 and DAG[54,55].			
LTD: Weakening of the synaptic strength due to a relatively low frequency stimulation of the synapses	Cerebellum, hippocampus, cerebral cortex	Ionotropic: NMDARs	Activation of pre-synaptic neuron sufficient to trigger a moderate response of NMDA receptors and does not require both synapses to be activated at the same time[51].	Deactivation of AMPARs involved in maintenance of LTD [131].	Suppressive nature of LTD more likely to be associated with quiescent state of sleep.	Interferes with LTP thereby providing a counteractive balance to prevent hyperexcitability of neurons[52].
		Metabotropic: GPCRs like mGlu1Rs, mGlu5Rs, GABA-B	Ionotropic induction requires moderate activation of NMDA receptors by glutamate for Ca^{2+} influx in post-synaptic neuron which is lower than that for LTP induction[52].	Requires activation of intermediate protein phosphatases like protein phosphatase 1, 2 and calcineurin by low Ca^{2+} concentration to inhibit the release of membrane obscured AMPARs[53].	More commonly linked with SWS associated cellular and molecular modulation of synaptic plasticity [64].	Involved in memory consolidation and learning: Weakened state of synapses implicated in forgetting old memories in order to make space for new ones [65]; Involved in novelty acquisition and spatial learning[66].
			Metabotropic induction through mGlu1Rs and mGlu5Rs causes endocytosis of the expressed AMPARs and/or a decrease in phospholipase C *via* reduced adenylyl cyclase activity[62].			
			Enhancement of GABA-B mediated inhibitory effects may result in LTD[63].			

GABA-B: Gamma-amino butyric acid-B; NMDA: N-methyl-D-aspartate; SWS: Slow wave sleep; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LTP: Long term potentiation; LTD: long term depression; mGlu: Metabotropic glutamate; 5-HT: 5-hydroxytryptamine.

acquisition[70] and experimental studies on rats that were exposed to hole board exploration resulted in events that reversed LTP upon exposure to a novel environment with inductive LTD mechanisms being activated. These rats showed habituation upon a second exposure to that environment indicating LTD's possible

role in remembering the previously acquired information of that environment[66]. On the contrary, work done on adult rats has also revealed the significance of LTD and LTP by demonstrating that the preservation of LTP is hampered upon an increase to LTD susceptibility and this also interrupts the CNS functions including learning and information retention[71,72]. Therefore, there are debatable influences of LTD on learning but its role in novelty acquisition and spatial learning[66,73] deserves further investigation.

What exactly is harnessing this LTP and LTD in these regions of the brain and how these activity dependent synaptic changes relate to memory consolidation and learning? In this review, an attempt is made to find some answers. An early hypothesis put forward by Lynch and Baudry[74] on the biochemistry of memory involved an examination of calcium proteinase-receptor interaction. They demonstrated that in the forebrain sub-synaptic membranes, an influx of Ca^{2+} causes a long lasting increase in the number of glutamate receptors through its activation of the enzyme calpain which is a proteinase. The activated form of this enzyme degrades the membrane-anchored cytoskeleton protein fodrin and as a result, exposes the obstructed glutamate receptors. The effects of this Ca^{2+} proteinase-receptor interaction could functionally modify neuronal circuits as well as showed similar biochemical effects that are seen post learning[74]. This and other related studies examining molecular mechanisms were, therefore, examined to find correlations between synaptic strength and memory consolidation.

Most work done on excitatory neurons like the hippocampal pyramidal cells reveal that tetanic stimulation of inputs can readily induce LTP that lasts for hours, days and can even be permanent, making it a good cellular correlate of memory and learning [75-77]. *In vivo* and *in vitro* induction of LTP and LTD through external theta burst stimulations in model organisms[47,49,78] has revealed the various cellular components that present themselves as functional entities in the process of memory formation and learning. It is already well established that receptors like metabotropic glutamate receptors (mGluR), ionotropic NMDA and AMPA receptors are mediators for LTP and LTD through the increase or decrease in the Ca^{2+} concentration, respectively[51,79,80]. Both ionotropic (*e.g.*, NMDA, AMPA receptors) and metabotropic (*e.g.*, mGluR) receptors are known to be involved in synaptic plasticity but project different mechanisms of action which are employed for mediating excitatory and/or inhibitory signals[81]. The ionotropic receptors are heteromeric compounds that consist of a ligand binding site and pore forming channel that combines the function of the receptor and ion channel into a single unit for the mediation of post-synaptic potentials. On the other hand, metabotropic receptors do not comprise of an ion channel but mediate their effects on other ion channels *via* intermediate effector molecules and secondary messengers. Ionotropic receptors like NMDA and AMPA receptors get activated upon binding of the neurotransmitter glutamate on the ligand-binding site and this leads to an opening of the ion channel subunit of the receptor which is permeable to Na^+ and K^+ ions to induce an inward current causing depolarization through the excitatory post-synaptic potential (EPSP) that lasts for a few milliseconds[51]. NMDA channel is permeable to the above cations and also to Ca^{2+} which affects the downstream signalling cascade that regulates synaptic plasticity[82]. Glutamate can also bind to the mGluRs which leads to an activation of signal transduction molecules like the receptor associated G-protein that gets detached from the receptor and directly activates the nearby ion channels like NMDA receptors or promotes the action of various effector molecules that indirectly activate other ion channels. mGluRs can also regulate the intracellular Ca^{2+} levels through membrane proteins and secondary messengers. The influx of ions through these receptors therefore results in post-synaptic potentials that have a slower induction and longer response time ranging from a few milliseconds to even much longer times[83]. LTP is known to be predominantly mediated by the ionotropic receptor NMDA when high frequency stimulations result in a build-up of EPSPs due to the activation of AMPA receptors causing the removal of a Mg^{2+} block of the NMDA channel[51,58]. However, metabotropic receptor mediated LTP has also been observed with mGlu1 and mGlu5 receptors wherein mGluR activation can lead to LTP induction through NMDA receptors as well as *via* the modulation of intracellular Ca^{2+} levels[84,85]. As mentioned before, LTD arises upon a lower frequency stimulation of the excitatory synapses than needed to induce LTP and also involves NMDA receptors but with a resulting deactivation of the AMPA receptors. LTD mediated by metabotropic receptors like mGluRs usually involves secondary messengers that modulate intracellular Ca^{2+} levels [62]. Other metabotropic GPCRs like gamma-amino butyric acid-B receptors (GABA-B Rs) can also induce LTD due to their inherent nature to transmit inhibitory signals[63]. The details of these molecular and cellular features of synaptic plasticity will be

discussed more in the coming sections. Since activity dependent synaptic plasticity and memory consolidation occur sequentially, cellular receptors and other associated molecules that mediate LTP and LTD consequently find themselves to be associated with learning and memory processing[61,86].

Significance of synaptic plasticity in sleep and sleep deprivation

The active state of sleep has been associated with many functions, including synaptic plasticity (LTP and LTD), cognitive learning and memory processing[87]. In fact, it is also reasonable to suggest that learning paradigms that promote sleep and synaptic plasticity also enhances brain development[57,88].

The above notions have risen from earlier hypotheses that sleep affects the patterns of neuronal circuits in the brain[42,89]. REM sleep is associated with long-term memory consolidation and learning events promote synaptic plasticity. Moreover, REM is required for brain development and an increase in intensive learning activity significantly enhances the duration and number of REM sleep cycles and promotes synaptic plasticity[90,91]. Correlating sleep cycles and synaptic plasticity, LTP has been credited with many learning functions of the brain, especially in the hippocampus. It appears that sleep deprivation results in an inhibition or decrease in the level of LTP and an impairment in the associated learning[92,93]. This trend has also been observed in rats during sleep fragmentation where in there was a decrease in LTP through NMDA receptors in the CA1 neurons of the hippocampus[94]. Interestingly, the reduction in LTP is also associated with a downregulation of cortactin, which is a dendritic cytoskeleton protein, pointing towards the role of LTP in the structural modification of neurons and a disruption upon sleep deprivation[95]. While the impact of sleep deprivation on LTP seems clear, the fate of LTD has not been adequately identified. However, LTD is known to protect neurons by regulating neuronal hyperexcitability and preventing a saturation of network activity[59]. Additionally, LTD's role in memory consolidation has been seen through events like novelty acquisition and spatial learning or even in making space for new memories through the concept of 'forgetting'[65,66,73]. Since these aspects of memory processing are sleep dependent, it is logical to suggest that sleep deprivation can affect LTD. In agreement with this line of thinking, an increase in hippocampal LTD following sleep deprivation was observed in rats[96].

In conclusion, sleep seems to promote synaptic plasticity, especially LTP, and memory consolidation, while sleep disturbances appear to adversely affect both. LTD seems to be enhanced following sleep deprivation and, thus, may be associated with interference with memory consolidation.

SIGNIFICANT REGULATORY MOLECULES IN SLEEP AND SLEEP DEPRIVED CONDITIONS

Molecular events in association with sleep and synaptic plasticity

After a brief introduction of a few cellular components involved in the functioning of synaptic plasticity in section II, some detailed events in relation to the state of sleep are described here. Going back to the fundamentals of electrophysiology, an electrical signal is transmitted when a neurotransmitter gets released from the pre-synaptic cell and activates its specific receptor on the post-synaptic cell. This further invites a series of downstream reactions that ultimately give rise to the required effect. Neurotransmitters and receptors are cellularly synthesized molecules and if the signal pattern changes during stages of sleep and wakefulness, changes in the expression of genes and proteins, that are precursors for these molecules, can also occur. In sleep and sleep deprivation, glutamate, acetylcholine, DA, serotonin, *etc.*, are important transmitters to pay attention to. Acetylcholine, for instance, is known to be correlated with the amplitude of theta burst oscillations that take place in the hippocampus. Events that lower the levels of acetylcholine can reduce the amplitude of such oscillations[97]. Since sleep sensitive processes of learning, like memory consolidation demonstrate oscillatory changes, neurotransmitters like acetylcholine are significant to such brain functions. Additionally, imbalances in the levels of neurotransmitters like DA and serotonin are associated with many neurogenic issues like depression, anxiety and psychosis; all of which are symptoms often seen in patients that have been sleep deprived[98-100].

Focusing more on the receptors involved in mediating synaptic plasticity in excitatory glutamatergic pathways, the glutamate receptors present themselves as

frontline players and amongst these, the ionotropic NMDA and AMPA receptors are known to depolarize/excite the post-synaptic neuron through an influx and efflux of Na^+ and K^+ ions, respectively[83]. The main inhibitory neurotransmitter of the CNS is GABA and it acts upon the two types of GABA receptors: Ionotropic GABA-A/GABA-C receptors and metabotropic GABA-B Rs. GABA's contribution to modulating LTP and LTD in excitatory pathways, owing to the strategic location of its receptors to regulate input and output signals in the pyramidal neurons, is well documented[101-103]. LTP and LTD are carried out by the long term excitatory and inhibitory actions of these receptors including GPCRs, which will be looked into in the next section. Ca^{2+} has been a crucial factor and its increase has shown to depend on the activation of NMDA receptors by glutamate, Ca^{2+} release from intracellular stores and its influx through the voltage gated calcium channels[104]. The binding of the released calcium to calmodulin and then further to two other proteins: Ca^{2+}/calmodulin dependent protein kinase type 2 (CAMK II) and calcineurin, results into LTP and LTD, respectively[104].

In continuation with the molecular changes associated with synaptic plasticity, protein synthesis and post-synaptic biochemical changes have been implicated in different phases of LTP[105]. For instance, brain derived neurotrophic factor, protein kinase Mζ, calcium/CAMK II, and activity-related cytoskeletal protein, have so far been indicated in the induction or maintenance of late phase LTP[106-109]. Whether these or other factors participate during sleep-induced consolidation of memory is unknown and needs future investigation. Another not so conventional molecule that is speculated to promote synaptic plasticity is nitric oxide (NO). What is intriguing about this molecule is that the enzyme which synthesizes it is activated by an increase in Ca^{2+} concentrations which again is dependent on receptors like NMDA which promotes synaptic plasticity[57,110]. More insight on such accessory molecules needs to be put forward through detailed experimental work and NO has so many other important physiological functions like decreasing vascular resistance and increasing cerebral blood flow and oxygenation rate[111] or playing a key role in mediation of an immune response against infectious diseases[112]. Thus, its definitive role in sleep deprivation through synaptic plasticity can be a major contribution to this field of research.

In summary, these are just few of many cellular components which have been discussed here to help understand and appreciate the intricate network of cellular molecules in driving synaptic plasticity which also play an important part in carrying out sleep associated functions. The functions carried out by these regulatory molecules have been known to get altered during the state of sleep and sleep deprivation. This means that the genes that transcribe the proteins for these receptor molecules also undergo changes. Differential gene expression has been observed during both the states of sleep and wakefulness. In fact, modulation in the gene expressions during these two states have shown that around 10% of the total cerebral cortex transcripts are differentially expressed[113]. For instance, the mRNAs for the receptors of the inhibitory neurotransmitter GABA, shows a higher expression during the state of sleep as compared to the state of wakefulness[113,114].

GPCRs

GPCRs by definition are receptors that mediate their effects after binding to G proteins which are heterotrimeric molecules made up of alpha, beta and gamma subunits that function by phosphorylating the nucleotide guanosine triphosphate to guanosine diphosphate. Structurally, GPCRs are transmembrane proteins with multiple transmembrane domains and the homology of these domains categorize them into 4 classes (A, B, C and F). About 90% of the non-sensory GPCRs are expressed in the brain and appear to play regulatory roles in various neurological processes. The expression profile of these receptors is extremely high in the hippocampus (around 300 GPCRs) and about 20 of these GPCRs display their potential role in synaptic plasticity [115]. The signalling pathways that are induced by the GPCRs regulate both pre and post-synaptic components which ultimately can affect synaptic plasticity as well as the release of pre-synaptic vesicular molecules[116]. They are also known to be involved in events of structural plasticity as well as cognitive development[117]. GPCRs can also alter NMDA receptors by a direct action at the CA1 synapses, thus indirectly affecting NMDA receptor-mediated synaptic plasticity[118], suggesting the possibility for receptor co-expression. Furthermore, GPCRs also seem to elicit their effects intracellularly while modulating synaptic plasticity[119]. The range of neuronal

functions that are attributed to GPCRs needs a more coherent and concrete investigation to be well defined in relation to sleep deprivation, synaptic plasticity and memory consolidation. For the purposes of this review, two major types of GPCRs known as the mGluRs and GABA-B Rs are discussed in more detail. Other GPCRs, especially those that are important for drugs used in psychiatry, are also discussed.

mGluRs

The mGluRs belong to the class C of GPCRs. They are categorized into three groups based on their signal transduction pathways. Group I (mGlu1R and mGlu5R), Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7, mGluR8)[120]. The subdivisions are based on the difference in their physiological activity and structure. The group I receptors display a post-synaptic location and are known to act *via* the Gq protein through the activation of phospholipase C protein and the synthesis of the secondary messengers such as inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG). The general pathway involving these secondary messengers results in the release of intracellular Ca^{2+} stores which is a prerequisite for the induction of synaptic plasticity[54,55]. These receptors are also involved in the modulation of neuronal excitability in the hippocampus pyramidal cells wherein they activate cationic conductance through the reduction in resting K^+ current and inhibition of Ca^{2+} ion channels[121,122]. On the other hand, mGluRs were also seen to induce IP3-mediated release of Ca^{2+} from intracellular stores through stimulation of CA3 pyramidal neurons. Unlike the Group I mGluRs, Group II and III mediate their functions *via* the Gi/Go protein. They are negatively coupled to adenylyl cyclase and inhibit the production of cyclic adenosine monophosphate Cyclic adenosine monophosphate (cAMP)[123] which results into activation of K^+ channels and inhibition of Ca^{2+} channels. These two groups have a very distinct pre-synaptic localization pattern with Group II being predominant in extra synaptic sites whereas Group III in the synaptic sites. Additionally, the Group III receptors also appeared to be segregated in correlation to their target post-synaptic neurons[124].

GABA-B Rs

The metabotropic GABA-B Rs are widely known for their inhibitory action in the CNS and like mGluRs, also belong to the class C GPCRs. Structurally, these are obligate heterodimers made up of GABA-B1 and GABA-B2 receptor subunits which are genetically co-expressed and are homologous to the structure of mGluRs[125,126]. Gene expression studies for this receptor have shown that heterodimerization is essential for the GABA-B Rs to elicit their function since the individual expression of the GABA-B1 subunit in the target mammalian cells results in immature and low functionality receptors as compared to the heterodimer[127]. These receptors show a wide cellular and sub cellular localization pattern through their expression on pre-synaptic, post-synaptic as well as extra synaptic regions in the brain[128]. Based on work performed on rat hippocampus, the two subunits of GABA-B Rs: GABA-B1a/b and GABA-B2, appear to be more on the post-synaptic regions as compared to the pre-synaptic ones. Furthermore, they also displayed an abundant distribution of GABA-B1a/b on glutamatergic synapses on the spines and on dendritic shafts of pyramidal cells[128]. GABA-B2 on the other hand, has a dominant extra-synaptic localization. These localizations are indicative of their functions and considering the range of cellular and subcellular occurrences of these receptors, they show a promising involvement in a great number of neurogenic processes. For example, their presence at the glutamatergic terminals points towards their involvement in glutamatergic neurotransmission[128].

Functionally, GABA-B Rs induce their slow and long lasting action *via* the Gαi/o proteins through the inhibition of adenylate cyclase and like the mGluRs, they too affect the Ca^{2+} and K^+ conductance[129]. GABA-B Rs are known to control the calcium dependent neurological processes through the inhibition of voltage sensitive Ca^{2+} channels[85,130]. On the pre-synaptic sites, GABA-B Rs appear to be negatively coupled to Ca^{2+} channels and block the Cav2.2 (N- type) and Cav2.1 (P and Q type) voltage gates channels *via* the action of G- proteins. They also have the ability to affect K^+ channel directly without the involvement of a G protein. This controls the release of neurotransmitters from the pre-synaptic neurons and thus GABA-B Rs have the potential to regulate the onset of a stimulatory signal[85,130]. At the post-synaptic sites, these receptors mediate their effects *via* the G proteins through a slow hyperpolarization by inward rectification of K^+ channels such as the GIRK channels as well as Ca^{2+} channels[131]. GABA-B Rs are, therefore, diverse both in their structural as well as functional mediation of inhibitory signals and show immense potential to regulate synaptic plasticity in association with sleep deprivation.

Serotonin, DA and norepinephrine receptors

The serotonin, DA and epinephrine group of GPCRs are very important in psychiatry considering their ligands are responsible for a wide range of CNS functions like cognitive learning and sleep-wake behaviours and are implicated in many neurological disorders. Serotonin receptors, also known as the 5-hydroxytyrptamine (5-HTA) receptors are classified into 7 families (5-HT1 to 5-HT7), all of which are GPCRs except the 5-HT3 receptor[132]. These are further divided into their respective 14 sub-types [*e.g.*, 5-hydroxytyrptamine subtype 1A (5-HT1A) to 5-HT1F] based on their function and location[132]. They exhibit their function mainly through the Gαi, G αq/11, and Gαs proteins followed by modulation of Ca^{2+} concentrations *via* the regulation of adenylyl cyclase and cAMP or activation of phospholipase C producing IP3 and DAG[133]. In the CNS, 5-HT1 and 5-HT5 are associated with inhibitory signal transduction and the others are excitatory in nature; with pre- and post-synaptic localizations. For instance, the 5-HT1A receptors, which are widely implicated in depression, anxiety and learning, are found in both pre-synaptic (auto-receptors) and post-synaptic (heteroreceptors) locations[134]. Additionally, structural significance in this class of receptor through dimerization with each other and other GPCRs has also been indicated as a functional prerequisite for the cellular trafficking and functioning of 5-HT receptors[135].

DA receptors are GPCRs divided into 5 subtypes (D1-D5) and exhibit their action through the Gs/olf and Gi/o proteins by activating or inactivating adenylyl cyclase, respectively[136]. These receptors have a wide pre and post-synaptic distribution pattern in the CNS which contributes to the functional significance of DA[137]. For instance, the D1 and D2 receptors are abundantly localized in the striatum and substantia nigra region of the brain and are involved in the nigrostriatal pathway which is responsible for the control of bodily movements[138]. These are also majorly distributed in the ventral tegmental area (VTA) of the brain which is connected to the ventral striatum and this connection promotes reward-associated behaviour *via* the meso-limbic pathway[139]. Furthermore, along with a localization pattern observed in both pre- and post-synaptic regions, co-expression is also a general trend seen with DA receptors[140]. Lastly, the GPCRs that are the target for the catecholamine norepinephrine/noradrenaline (NA) are classified into alpha-1, alpha-2, beta-1, beta-2 and beta-3 receptors and they are localized on both pre- and post- synaptic sites. Alpha-1 follows the Gq protein mediated elevation of calcium levels by activation of phospholipase C producing IP3 and DAG and the other three subtypes work *via* the modulation of adenylyl cyclase pathway[141]. Interestingly, co-localization patterns have also been observed between DA and NA receptors in the rat prefrontal cortex [142]. Whether such co-localizations and/or dimerization have implications for pharmacological actions of therapeutic agents need further investigation.

SIGNIFICANCE OF GPCRS IN SYNAPTIC PLASTICITY AND SLEEP DEPRIVED CONDITION

Role of GABA-B and mGluRs

As introduced above, GPCRs appear to be involved in processes that regulate the transduction of action potential especially in the cells of the hippocampus region of the brain. Both LTD and LTP have demonstrated a pattern of being modulated by such regulatory molecules. It is already well established that Type I mGluRs induce LTD through the synaptic endocytosis of AMPA receptors in the hippocampus[143]. Similar lines of studies have pointed towards mGluRs in the CA1 pyramidal cells being involved in the induction of LTD through post-synaptic elevation of Ca^{2+} levels[144]. Interestingly, studies on the cerebellar Purkinje fibres have also demonstrated that activation of GABA-B Rs enhances LTD through an association with mGluRs[63]. Even though the mechanism of action of these receptors may be related, many of their molecular machineries have their own distinctive features while promoting cellular LTD. For instance, in the Purkinje fibres, LTD mediated *via* GABA-B relied on the beta gamma subunits of the G-protein whereas mGluR mediated LTD depended on the alpha subunit[63]. So far, it appears that these GPCRs are associated with the induction of LTD and reviewing other related studies, we know that NMDARs are the main mediators of LTP. Contrary to these findings, recent experimental work has put forward a type of LTP that is induced in the absence of NMDARs and requires the activation of Type I mGluRs[145]. As for the role of GABA-B Rs in LTP, its auto receptors depress their own activity through negative feedback and promotes

NMDAR mediated LTP, thus maintaining a balance between LTP and LTD[146]. Considering how the hippocampus and the cortex communicate and manifest their functions of learning and memory consolidation in the state of sleep through synaptic plasticity, it is reasonable to imply that these GPCRs modulating LTD and LTP are significant for this purpose. It also seems that co-expression of GPCRs and their heteromeric subunits is a repeated trend seen in studies that show the association of GPCRs with LTD[63,125,126]. The functionality of GPCR dimerization has also been put forward in earlier demonstrative studies which showed that the GABA-B1 subunit needs the GABA-B2 subunit to reach the cell surface and that GABA-B1 is responsible for agonist interaction whereas the B2 subunit works towards the G-protein activation [147,148]. Furthermore, gene knock-out or elimination studies for these subunits have also indicated the dependence on dimerization for the functioning of this receptor and that in some regions of the brain, GABA-B subunit gene elimination does not affect the functionality of the receptor which implies that it is replaceable by other G-protein activating molecules[149] and thus may have the potential to associate with other GPCRs to mediate their actions. Progressing from these initial findings, recent work done on rats that were sleep deprived using gentle prodding and tapping has demonstrated that induced LTD of population EPSP in the hippocampus requires activation of mGluRs and GABA-B Rs along with an increase in Ca^{2+} released from intracellular stores[150]. In sleep deprived conditions, western blot analysis and co-immunoprecipitation studies revealed that there were elevated expression levels of mGlu1αR and GABA-B1 receptor subunit as well as enhanced co-expression and heterodimerization between mGlu1αR and GABA-B R1 subunit and mGlu1αR and GABA-B R2 subunit[150].

Role of 5-HT and other GPCRs

As introduced earlier, GPCRs for serotonin are diverse both in their localization and functions. Their effects are mediated by calcium levels, which again is crucial for synaptic plasticity. Furthermore, 5-HT1A receptors are known to decrease NMDA receptor activity whereas 5-HT2A tends to increase it[151,152], thereby playing an opposing role in regulating NMDA mediated LTP. These are also co-expressed in hippocampal pyramidal cells and may direct studies towards their reciprocal action in regulating synaptic plasticity. Similar cross-talks have also been suggested between 5-HT and GABA-B receptors[153], which as already discussed, are involved in modulating LTD, especially in sleep deprived conditions. In relation to sleep associated studies, 5-HT1 and 5-HT2 receptors appear to be involved in the regulation of REM sleep and sleep-wake behaviours[154]. To further strengthen the significance of these receptors, experimental work has indicated that sleep deprivation resulted in a temporary increase in the expression profile of the serotonin receptor, 5-HT1A through an enhanced suppressive effect of this receptor on the EPSPs recorded from CA1 pyramidal neurons[155]. Studies also indicated a heterodimerization of 5-HT2A-mGluR2 which is implicated in psychosis[156]. However, in rat hippocampus, while there was a change in the expression profile of 5-HT1A receptor, there was no significant heterodimerization with mGluRs following sleep deprivation[155]. Therefore, depending on the 5-HT receptor sub-type, it appears that sleep deprivation induces differential changes in their expression, co-localization and heterodimerization.

DA and NA receptors demonstrate somewhat analogous modulations of synaptic plasticity. In rat prefrontal cortex, DA receptors appear to modulate both LTD and LTP through glutamatergic synapses[157]. In the hippocampus, opposing effect of D1/D5 and D2/D3/D4 receptors on NMDA receptor modulation, regulates LTD and LTP [158]. Furthermore, D1/D5 have also been implicated in novelty acquisition through hippocampal LTD and LTP[159]. The induction of synaptic plasticity *via* NA receptors is more prevalent through the beta group receptors and they do so by modulating both NMDA and AMPA receptors in the pyramidal cells and perirhinal cortex[158,160]. Consequently, the modulation of synaptic plasticity *via* DA and NA receptors can be extended towards sleep associated functions. Studies in rats have indicated that sleep deprivation leads to a differential expression of DA receptors[161] and chronic sleep restriction results in changes in the density of NA receptors[162]. Considering the range of these GPCRs and their functions, their cross-talk properties and effects during the state of sleep through synaptic plasticity require further detailed investigation.

Allosteric modulation of GPCRs

Another intriguing and related aspect of GPCRs that signifies its structural implications in synaptic plasticity is the allosteric modulation of these receptors. Binding at sites other than the active site of the GPCR, it has been suggested that allosteric

modulators can selectively stimulate the homomeric and heteromeric forms of the receptor. For instance, in the CNS, heterodimerization is seen between mGlu2R and mGlu4R with allosteric modulation being targeted to the homomeric forms relative to the heteromeric receptors[163,164]. Furthermore, LTP and LTD and spatial learning at the excitatory synapses in the hippocampus have appeared to be enhanced by the positive allosteric modulation of mGlu5Rs[165]. Considering even GABA-B receptors demonstrate their sleep dependent synaptic changes by forming such heteromeric complexes and associations with mGluRs[150], the importance of such structural modifications and associations needs more attention with respect to sleep dependent functions.

DISCUSSIONS

Sleep is important for normal physiological and neurological functions and sleep deprivation affects majority of these functions. The negative effects of sleep deprivation can be better managed when we are able to specifically target the cellular and molecular machinery that drives these functions and, in this review, GPCRs are examined as a pivotal molecular machinery that impacts sleep associated functions through synaptic plasticity. For example, memory consolidation and learning as a model involving hippocampal-neocortical dialogue was looked at. The dialogue, in turn brings forth distinct electrophysiological patterns that are active during the SWS and REM sleep stages. Activity mediated synaptic plasticity has been widely correlated to sleep associated functions of cognitive learning, memory processing and over all brain development. GPCRs like GABA-B Rs and mGluRs are types of receptors that have shown a potential to be involved in these processes through their actions on LTD and LTP. What is even more intriguing is the fluctuation in their distribution, heterodimerization and co-localization following sleep deprivation, suggesting that these receptors can exist in one condition during normal sleep and change with sleep deprivation. GPCRs are one of the major cellular targets for drug interaction and therefore changes in the receptor expression profile can affect drug action.

For instance, the antipsychotic drug clozapine is one of the common and effective drugs used in treating disorders like schizophrenia. The cellular targets for this drug are GPCRs like 5-HT2A and DA D2 receptors with a higher affinity for the former receptor than the latter. It acts as an antagonist of DA D2 receptors in the mesolimbic pathway and although initially classified as an antagonist, clozapine is also known to be an inverse agonist of the 5-HT2A receptor present in the prefrontal cortex of the brain[166-168]. Other antipsychotic drugs like olanzapine, risperidone, aripiprazole, *etc.*, have also been indicated to elicit their effects through these receptors[166]. Interestingly, 5-HT2A and mGluR2 receptors are suggested to form heterodimers which raise the possibility of testing if clozapine and other such antipsychotic drugs modulate similar complex formation[156]. Moreover, drugs like clozapine are known to have sleep-inducing effects[169] and since disorders like schizophrenia and other psychiatric diseases are associated with sleep disturbances[170], potential interplay between the molecular events of sleep deprivation and actions of antipsychotic drugs needs to be investigated. Other examples of drugs that act on GPCRs include ropinirole for Parkinson's disease which acts as an agonist on DA D2 receptors[171] and baclofen, a GABA-B receptor agonist suggested for treatment of depression and anxiety[172]. Whether their actions change with sleep deprivation and *vice versa* also needs to be tested. With regards to synaptic plasticity, antipsychotics and antidepressants are suggested to affect LTP upon both acute and chronic use and interestingly, these effects are different for each of these situations which may suggest differences in network behaviour with acute *vs* chronic exposure to the drugs (see Table 2[173-211]). Moreover, their effect on LTD has not been sufficiently explored and hence similar studies on the differential effects of chronic *vs* acute use of such drugs on network behaviour are required with regards to LTD. Table 2 provides a brief summary on antipsychotic, antidepressant and anxiolytic drugs with their mechanisms of action and association with synaptic plasticity, learning and sleep.

The relation between a drug's mechanism of action and sleep can be directly observed in drugs that are used for treating sleeping disorders like insomnia. Characterized by a lack of both quality and quantity of sleep, insomniac conditions are treated with many drugs that target GPCRs. For example, melatonin is a hormone that has been known to play a key role in the sleep-wake cycle and promoting sleep. Agonist drugs like ramelteon act on the melatonin GPCRs type 1 and 2 (MT1 and MT2) which results in reduced sleep latency in chronic insomniac patients[212].

Table 2 Changes in synaptic plasticity, learning and sleep associated with antipsychotic, antidepressant and anxiolytic drug therapy

Class of drugs	Drug examples		Target GPCRs	Mechanism of action	Therapeutic application	Possible association with synaptic plasticity and learning	Implications in sleep and associated functions
Antipsychotics	1st generation / typical antipsychotic drugs	Chlorpromazine	DA D1/D2/D3, 5-HT2A, Histamine H1, α1-Adrenergic, Muscarinic receptors.	1 Acts as an antagonist by blocking post-synaptic DA D2 receptors.	1 In the treatment of psychotic disorders like schizophrenia, bipolar disorder, acute mania, dementia, *etc*.	1 Synaptic plasticity: Acute treatment with haloperidol can impair induction of LTP but not its maintenance in rabbit hippocampus. Chronic treatment with haloperidol suggested to enhance LTP in corticostriatal brain slices of rats[174,175].	1 Associated with sedation and often promote sleep inducing effects.
		Haloperidol		2 Can also block serotoninergic, histaminergic, cholinergic and noradrenergic receptors[173].	2 Reduce psychosis symptoms like hallucinations and delusion.	3 Learning Functions: Haloperidol and Chlorpromazine can impair spatial learning in rats[176,177].	(1) Haloperidol, loxapine and mesoridazine increase REM sleep latency. Withdrawal of drug causes significant disruption of sleep with reduced REM and total sleep;
		Loxapine					(2) No significant effect on SWS[178-180];
		Mesoridazine					(3) Chlorpromazine enhances SWS along with a dose dependent effect on REM sleep - lower doses increasing and higher doses reducing or having no effect on REM sleep[181].
	2nd generation /atypical antipsychotic drugs	Clozapine	DA D2, 5-HT2A, 2C receptors	1 Antagonistic effects by blocking 5-HT2A/2C receptors and agonistic effects by promoting 5-HT1A receptor mediated actions.	1 In the treatment of psychotic disorders like schizophrenia, bipolar disorder, acute mania, dementia *etc*.	1 Synaptic Plasticity: Without tetanization, acute clozapine administration induces LTP in rabbit hippocampus[184]. Chronic treatment with clozapine impairs LTP in rat prelimbic cortex [185]; Acute administration of risperidone impairs LTP in rabbit hippocampus. LTP induction post tetanization takes places in rat hippocampus upon chronic treatment with olanzapine[186,187].	1 Associated with an increase in the total amount of sleep but show an uneven trend in their stage specific effects.
		Risperidone Olanzapine		2 Transiently block DA D2 receptors [182].	2 Reduce psychosis symptoms like hallucinations and delusion, disordered thinking, social withdrawal *etc*.	2 Learning Functions: Clozapine and olanzapine impair memory retrieval in mice[188] while risperidone improves learning and memory processing in humans [189].	(1) Clozapine increases REM sleep density and improves NREM sleep. However, its effect on SWS is inconsistent[180];
	3rd Generation	Aripiprazole	DA D2 receptors	1 Partial agonist of DA D2 and 5-HT1A			(2) Olanzapine improves SWS as

	antipsychotic drugs			receptors and an antagonist of 5-HT2A receptors. 2 DA D2 antagonist in the mesolimbic pathway[183].			well as REM sleep latency. Risperidone increases SWS but reduces REM sleep [180,190,191].
Antidepressants and anxiolytics		Fluoxetine	5-HT-1A receptors	1 Blocks the serotonin reuptake and increases serotonin action *via* 5-HT1A receptors. 2 Suggested to cause reversible internalization of 5-HT1A auto - receptors[192].	In the treatment of depression, obsessive control disorders, eating disorders, substance use disorders *etc*.	1 Synaptic Plasticity: (1) Acute treatment with fluoxetine before stressful stimuli indicated to suppress stress induced LTD in CA1 region of rat hippocampus[194]; (2) Chronic fluoxetine treatment enhances neurogenesis dependent LTP in mice hippocampal granule cells and also upregulates Brain-Derived Neurotrophic Factor-LTP associated genes. Acute treatment showed no such upregulation[195,196];	1 Associated with uneven side effects on sleep like somnolence, sedation and insomnia. (1) Fluoxetine reduces overall sleep continuity with a reduction in REM sleep but increases REM latency. It either increases or has no effect on SWS[197];
		Mirtazapine	5-HT1 and 2 receptors, α 2-adrenergic receptors	1 Blocks 5-HT2 receptors in order to increase 5-HT1 mediated transmission. 2 Antagonist of α2-adrenergic receptors to increase adrenergic neurotransmission [193].		(3) Acute treatment of vortioxetine enhances LTP in the CA1 region of rat hippocampus by increasing pyramidal cell output[199];of memory processing [207,208]; (4) Acute treatment of buspirone as an agonist of 5-HT1A results in the reversal of LTP in a time -dependent manner in rat hippocampal slices [202];	(2) Mirtazapine increases sleep continuity and SWS but does not affect REM sleep [197]; (3) Vortioxetine causes a reduction in REM sleep but increases its latency. It's effects on SWS are unclear [197];
		Vortioxetine	5-HT1A, 1B, 1D, 5-HT7 receptors.	Antagonist of 5-HT1D and H-HT7 receptors and a partial agonist of 5-HT1A and 1B receptors[198].	In the treatment of Major Depressive Disorder.	(5) Acute treatment of baclofen induces GABA-B receptor mediated LTD enhancement of a glutamate-evoked current in the cerebellar cortical neurons. It also enhances mGluR1-coupled intracellular Ca^{2+} release[63].	(4) Vilazodone causes sleep disturbances with a decrease in REM sleep and an increase in wakefulness and SWS[209];
		Vilazodone	5-HT1A receptors	Blocks the serotonin reuptake inhibitor and also acts as a partial agonist of 5-HT1A receptor and stimulates it[200].		2 Learning Functions: (1) Fluoxetine reverses memory impairment in rats and enhances memory processing in mice[203,204]. Chronic use of mirtazapine and vortioxetine improve cognitive functions in humans[205,206,208, 209];	(5) Buspirone increases REM sleep density and latency[210];
		Buspirone	5-HT1A, DA D2 auto receptors	Partial agonist of 5-HT1A receptor and antagonist of DA D2 auto receptors with low affinity[201].	For treating of Generalized Anxiety Disorder and side effects of	(2) Buspirone and baclofen are implicated in the impairment of memory processing [207,208].	(6) Baclofen prolongs total sleep time with an increase in duration for REM

			Parkinson's and Alzheimer's disease.	sleep and SWS [211].
Baclofen	GABA-B receptors	GABA-B agonist to increase inhibitory signals[172].	Suggested use in treating depression and anxiety as well as a muscle relaxant.	

LTP: Long term potentiation; LTD: long term depression; SWS: Slow wave sleep; 5-HT: 5-hydroxytryptamine; GABA-B: Gamma-amino butyric acid-B.

Intriguingly, the MTI and MT2 receptors have been known to form dimers among themselves as well as heterodimers with other GPCRs like the serotonin 5-HT2C receptor[213,214]. Thus, differences in ligand selectivity for these homomeric and heteromeric forms of the target receptors can have important consequences if the expression profile of such GPCRs change upon sleep deprivation. Other drug targets for insomnia include neuropeptides like orexins which promote wakefulness and are synthesized by neurons in the hypothalamus region of the brain. Drugs like suvorexant act as antagonists of the orexin GPCRs type 1 and 2 (OX1R and OX2R) thereby blocking their wakefulness promoting effects[215]. These GPCRs known to be associated with other GPCRs like the cannabinoid receptor type 1 (CB1) and GABA-B receptors. They form heterodimers with the CB1 receptors[216] which have been implicated in affecting memory formation and maintenance of mood. Moreover, orexin and GABA-B receptor activity are indicated to have a balancing interplay wherein inhibitory GABA-B modulates the wakefulness promoting properties in the orexin producing neurons[217]. If expression profiles of GABA-B receptors change with sleep deprivation, can there be consequences for actions of orexins? In summary, changes in receptor profiles associated with sleep deprivation can have consequences for drug action and need a thorough investigation to understand the mechanisms involved so that CNS disorders can be treated with more rationally based therapeutics.

Unlike receptor redistribution and co-localization, heterodimerization can have serious implications for drug-receptor interactions and consequently, its action. On the other hand, if co-localization of different receptors leads to common transduction pathways, it can significantly affect the actions of such drugs. These consequences can vary depending on whether pre- or post-synaptic receptors are changed with sleep deprivation. Since this process is dynamic and the receptors may be in different states, an understanding of the mechanisms involved in clearly needed. Moreover, since GPCRs among 5-HT, norepinephrine, DA, *etc.*, may be affected, drug therapy involving antidepressants and antipsychotics should take the occurrence of receptor plasticity with sleep deprivation into account as drug-receptor interactions may be changed (Figure 1).

FUTURE SCOPE

The diverse nature of GPCRs, both in their structure and functions has made them front line players in understanding many cellular processes. With the advent of sleep being credited with a wide range of psychological and physiological functions, and with changes happening in GPCRs following sleep deprivation, it is important to understand how the receptors and the functions they regulate, like synaptic plasticity and memory consolidation, are affected. GPCRs are one of the largest groups in the mammalian CNS. In psychiatry, most currently used antidepressants and antipsychotics act on one or more GPCR groups. Since the receptors change with alterations in sleep, unless the mechanisms involved in the change are understood, therapeutics will continue to suffer.

Potential research of cellular and molecular mechanisms

Firstly, even though LTP and LTD have both been emphasized in manifesting the neurological changes during the state of sleep and wakefulness, more work is needed with regards to LTD. In an attempt to bridge that gap, a better understanding of the inhibitory GPCRs like GABA-B receptors is highly crucial. Additionally, GABA-B and mGluRs seem to have an associative mode of action and based on the studies that are reviewed so far; it appears that co-localization and heterodimerization of these two

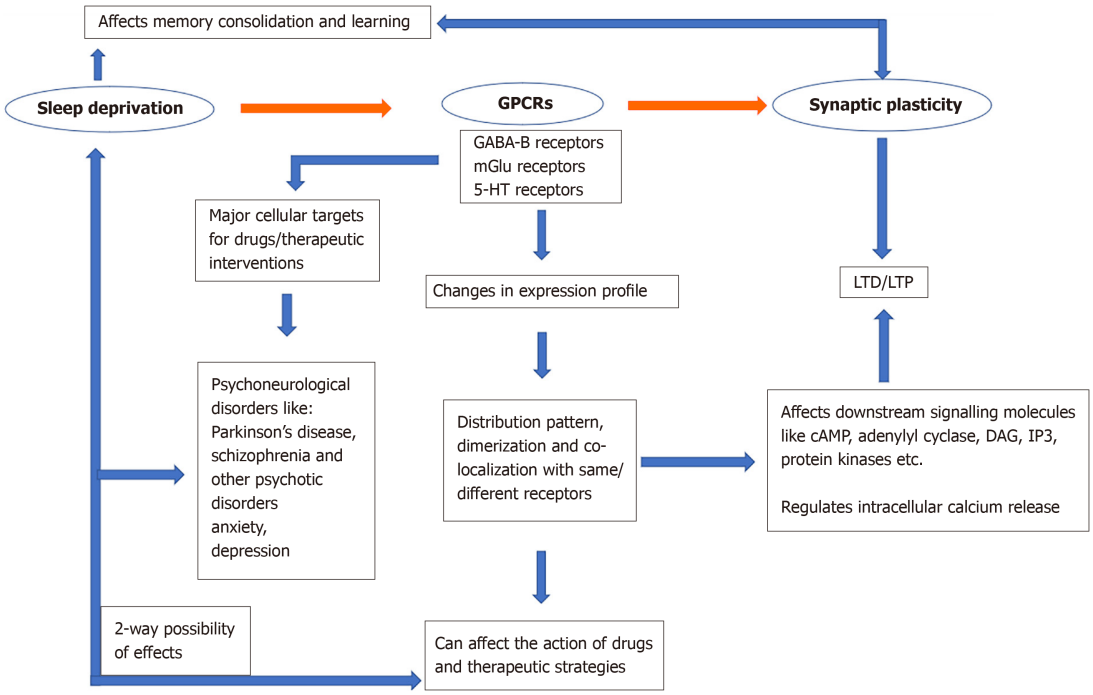


Figure 1 G-protein coupled receptors: Potential key-players in psychiatric therapeutics through modulation of synaptic plasticity in sleep deprivation. A correlation between sleep deprivation, G-protein coupled receptors (GPCRs) and synaptic plasticity. Memory consolidation and learning are strengthened during sleep and synaptic plasticity, through long term potentiation (LTP) and long term depression (LTD), can regulate the processing of these functions. Upon sleep deprivation, GPCRs like gamma-amino butyric acid-B, metabotropic glutamate and 5-hydroxytryptamine receptors experience changes in their expression profiles in terms of distribution, dimerization and co-localization with their own or different subtypes of receptors. Changes in these and the associated transduction pathways can in turn affect LTP and/or LTD, causing alterations in neuronal network activity. Since GPCRs are one of the most dynamic cell membrane proteins, they are the targets of many drugs used in various psychoneurological disorders. Therefore, a change in the expression profile of these receptors through sleep deprivation can reasonably alter the way in which these drugs exhibit their therapeutic action. Conversely, therapeutic strategies themselves can affect sleep causing a change in the GPCR expression profile and the downstream cascade. GPCR: G-protein coupled receptors; GABA-B: Gamma-amino butyric acid-B; LTD: Long term depression; LTP: Long term potentiation; mGlu: metabotropic glutamate; 5-HT: 5-hydroxytryptamine; cAMP: Cyclic Adenosine Monophosphate; DAG: Diacylglycerol; IP3: Inositol-1,4,5-triphosphate.

specific receptor types occurs with sleep deprivation[150]. Hence, the driving molecular factors which includes, specific genes and protein interactions, need a more coherent identification. For instance, the signalling linked with GPCRs are tightly controlled by a family of regulator of G protein signalling proteins in the brain[218]. Furthermore, since metabotropic receptors (*e.g.*, mGluRs) affect the function of ionotropic receptors like NMDA and AMPA, similar studies can be extended for the metabotropic GABA-B receptor and its ionotropic counterparts like GABA-A and GABA-C in relation to sleep deprivation induced changes. Considering that GPCRs are involved in several CNS functions, there is a wide scope for studying the mechanisms involved in their plasticity. Another interesting area of research is the regulation of synaptic plasticity by GPCRs elicited intracellularly[119] and this could also be explored further in order to connect the transportation of GPCR subunits from intracellular compartments to the cell membrane and the processes that take place in these compartments which can give rise to heterodimers and co-localization.

Future scope for psychoneurological disorders and therapeutics

Apart from memory consolidation and learning, GPCRs are also implicated in other psychoneurological occurrences. Around 60% of drugs target membrane proteins and 30% of them are GPCRs[219]. They are especially important as targets for antipsychotic and antidepressant drugs, considering some of their ligands like serotonin, DA and norepinephrine are associated with pathways that are important in psychiatry. Additionally, mGluRs and GABA-B Rs have an almost ubiquitous involvement in major cellular pathways which need to be better understood since they are affected in neurological disorders like Alzheimer's disease, Parkinson's disease, stress related disorders, *etc.*[220,221]. Changes in sleep patterns are often observed in many neurological disorders and considering these major GPCRs are altered during the state of sleep, an understanding of this correlation can affect the way we approach therapeutics in this area. For example, even though there was a temporary elevation

observed in the expression of the serotonin 5-HT1A receptor upon sleep deprivation [155], it is universally correlated to disorders like depression, anxiety and psychosis and changes in its expression profile upon sleep deprivation does warrant for further studies on this GPCR and its other subtypes. Additionally, related GPCRs like the DA receptor D1 are also known to interact directly with LTP inducing NMDA receptors [118] which are important in many neurological disorders. Furthermore, since the D1 and D2 DA receptors are involved in the nigrostriatal and mesolimbic pathways, changes in their expression profiles affect movements and behavioural patterns that are also implicated in Parkinson's disease and schizophrenia[222,223]. Therefore, DA GPCRs are highly potential drug targets and sleep associated changes in their expression profile needs more attention. Drugs used in psychiatry for such disorders, *e.g.*, aripiprazole, are known to target 5-HTA and DA receptors[224] and if the expression profile of these receptors is changing upon sleep deprivation, could it also affect the action of such drugs? Disorders like schizophrenia and depression often encompass sleep deprivation and drugs used for these conditions which target such GPCRs, may get negatively affected if receptor plasticity (co-localization and/or heterodimerization with other receptor subunits, *etc.*) occurs with associated sleep disorders. For example, the antidepressant drug mirtazapine exhibits its action through GPCRs by blocking 5-HT2 and adrenergic α_2 receptors, leading to an increase in the activation of 5-HT1A receptor mediated activity as well as NA release, respectively[193]. This drug is known to have sleep-promoting properties and has been associated with problems like day-time somnolence[225] potentially disrupting the normal sleep cycle. Interestingly, there are off-label therapies that employ antidepressants like mirtazapine in treating sleeping disorders due to its sedative effect[226]. Since antidepressants and antipsychotic drugs appear to directly or indirectly change activity at GPCRs, drug therapy for these disorders can affect sleep while sleep disturbances can also necessitate changes in that therapy. Therefore, sleep disturbance-induced plasticity and cross-talk between GPCRs can have consequences for drug therapy, the mechanisms for which need to be thoroughly examined. Lastly, allosteric modulation, which is another upcoming molecular interaction that is important for drug designing, can be applied to the homo and heterodimerization of GPCRs for various conditions. Hence, studies on structural, functional, receptor co-localization and remodelling, *etc.*, will yield new insights into mechanisms involved and help improve therapeutics for a variety of CNS disorders, including in psychiatry.

CONCLUSION

Conclusion and future scope are included in the main text under heading "Introduction" above.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 981-996

DOI: 10.5498/wjp.v11.i11.981

ISSN 2220-3206 (online)

REVIEW

Agmatine as a novel candidate for rapid-onset antidepressant response

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Author contributions: All the authors performed the literature search and wrote the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico, No. 310113/2017-2; and the CNPq Research Productivity Fellowship.

Country/Territory of origin: Brazil

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in

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Abstract

Major depressive disorder (MDD) is a disabling and highly prevalent mood disorder as well as a common cause of suicide. Chronic stress, inflammation, and intestinal dysbiosis have all been shown to play crucial roles in the pathophysiology of MDD. Although conventional antidepressants are widely used in the clinic, they can take weeks to months to produce therapeutic effects. The discovery that ketamine promotes fast and sustaining antidepressant responses is one of the most important breakthroughs in the pharmacotherapy of MDD. However, the adverse psychomimetic/dissociative and neurotoxic effects of ketamine discourage its chronic use. Therefore, agmatine, an endogenous glutamatergic modulator, has been postulated to elicit fast behavioral and synaptogenic effects by stimulating the mechanistic target of rapamycin complex 1 signaling pathway, similar to ketamine. However, recent evidence has demonstrated that the modulation of the NLR family pyrin domain containing 3 inflammasome and gut microbiota, which have been shown to play a crucial role in the pathophysiology of MDD, may also participate in the antidepressant-like effects of both ketamine and agmatine. This review seeks to provide evidence about the mechanisms that may underlie the fast antidepressant-like responses of agmatine in preclinical studies. Considering the anti-inflammatory properties of agmatine, it may also be further investigated as a useful compound for the management of MDD associated with a pro-inflammatory state. Moreover, the fast antidepressant-like response of agmatine noted in animal models should be investigated in clinical studies.

Key Words: Agmatine; Fast-acting antidepressants; Ketamine; Major depressive disorder; Microbiota-gut-brain axis; Neuroinflammation

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Received: March 2, 2021
Peer-review started: March 2, 2021
First decision: June 5, 2021
Revised: June 9, 2021
Accepted: August 23, 2021
Article in press: August 23, 2021
Published online: November 19, 2021

P-Reviewer: Bernstein HG
S-Editor: Zhang H
L-Editor: A
P-Editor: Yu HG



Core Tip: One of the main challenges in the advancement of antidepressant therapy is the establishment of safe and effective fast-acting antidepressants. Ketamine is a prototype for rapid-onset antidepressant responses. Agmatine has been shown to produce fast antidepressant-like effect by stimulating mechanistic target of rapamycin complex 1 signaling pathway, similar to ketamine. Moreover, NLR family pyrin domain containing 3 and microbiota-gut-brain axis may be novel targets for fast antidepressant responses. These targets have also been postulated to play a role in the antidepressant effect of both ketamine and agmatine.

Citation: Valverde AP, Camargo A, Rodrigues ALS. Agmatine as a novel candidate for rapid-onset antidepressant response. *World J Psychiatr* 2021; 11(11): 981-996
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/981.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.981

INTRODUCTION

Major depressive disorder (MDD) affects more than 300 million people and is a major cause of disability and suicidal deaths worldwide[1]. Despite the high prevalence of this psychiatric disorder, its neurobiological basis remains to be fully elucidated, and its treatment remains a challenge. Although the monoaminergic hypothesis of MDD has played a crucial role in its pharmacotherapy, it is now considered overly simplistic [2]. One of the limitations of this hypothesis is the fact that the drugs currently used to treat MDD exert their therapeutic effect only after 3-4 wk and many patients fail to respond to these drugs. Antidepressants also feature side effects that may include nausea, dizziness, insomnia, weight gain, sleep disturbances, and sexual dysfunction. This scenario underscores the strong demand for developing novel antidepressants with a fast antidepressant response, better efficacy, and fewer adverse effects[3,4].

In this regard, the year 2000 marked a turning point in the history of MDD pharmacotherapy, and Berman *et al*[5] showed for the first time that a single dose of ketamine, an N-methyl-d-aspartic acid (NMDA) receptor antagonist, produced a fast-acting antidepressant response in MDD patients. This discovery was reinforced by several subsequent studies that demonstrated that a single dose of ketamine elicited rapid and long-lasting antidepressant effects, even in treatment-resistant patients with suicidal ideation[6-8]. Although the discovery of ketamine is considered the major breakthrough in MDD pharmacotherapy and opened new perspectives to manage refractory patients at risk of suicide, ketamine has knock-on effects that limit its widespread clinical use[9]. For these reasons, ketamine has emerged as a prototype for screening novel fast-acting antidepressant agents. Agmatine, an endogenous neuromodulator, shares some common molecular mechanisms with ketamine and the ability to elicit fast antidepressant-like effects in preclinical studies[10]. Therefore, agmatine could be a novel candidate to elicit fast antidepressant responses.

Therefore, this narrative review presents evidence that agmatine has a rapid antidepressant effect and provides an overview of the possible mechanisms underlying this effect versus those already described for ketamine. The PubMed, SCOPUS, and SciSearch databases were searched for original manuscripts and contemporary reviews published in English.

KETAMINE AS A PROTOTYPE RAPID-ACTING ANTIDEPRESSANT AGENT

A milestone for the development of drugs with a rapid antidepressant effect has emerged over the past two decades[5,6]. Berman *et al*[5] demonstrated for the first time that a single subanesthetic dose of ketamine elicited fast (within 4 h) and long-lasting (for up to 3 d) antidepressant effects in MDD patients. These findings were reinforced and extended by Zarate *et al*[6], who showed that a single dose of ketamine effectively improved the MDD symptoms in treatment-refractory patients, as evidenced by an effect observed within 110 min that was sustained for up to 7 d. Importantly, a rapid resolution of suicidal ideation after a single infusion of ketamine in patients with treatment-resistant MDD was also observed, supporting the premise that ketamine has

rapid beneficial effects even in severely depressed individuals at risk of suicide[7,8]. Due to the ability of ketamine to alleviate MDD symptoms, several research groups have investigated its underlying molecular mechanisms.

Although ketamine has been well characterized as an NMDA receptor antagonist, its molecular effects extend far beyond this level. It is worth noting that this drug has a window of therapeutic efficacy that surpasses its short half-life of a few hours[11,12]. Experimental studies have provided evidence that the antidepressant-like effect of ketamine depends on mechanistic target of rapamycin complex 1 (mTORC1) activation, a key pathway required for protein synthesis–dependent synaptic plasticity [13-15]. It has been postulated that ketamine, by antagonizing NMDA receptors in GABAergic interneurons, attenuates the inhibitory action of this system on glutamatergic tonus. This blockade causes the disinhibition of pyramidal cells, which causes a burst of glutamatergic transmission[11]. In particular, the glutamate released under these conditions preferentially stimulates alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid (AMPA) receptors, promoting a transient sodium influx that depolarizes the cell and activates the voltage-dependent calcium channels (VDCC). This event causes the exocytosis of synaptic vesicles containing the brain-derived neurotrophic factor (BDNF) in the synaptic cleft, as a result of calcium influx by VDCC [16].

BDNF activates tropomyosin receptor kinase B (TrkB), which stimulates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mTORC1 signaling pathway[12]. In turn, mTORC1 controls the translation of proteins involved in new dendritic spine formation and synaptogenesis [*e.g.*, postsynaptic density protein-95 kDa (PSD-95), glutamate AMPA receptor subunit 1 (GluA1), and synapsin] by activating the 70-kDa ribosomal protein S6 kinase (p70S6K) and inhibiting the eukaryotic initiation factor 4E-binding protein[13,14,17]. Although mTORC1-dependent synaptogenesis induced by ketamine was first demonstrated in the prefrontal cortex of rodents[13,15], it has been shown that similar events also occur in the hippocampus[18-20]. Therefore, these findings suggest that targeting the mTORC1-driven signaling pathway may produce rapid-onset and long-lasting antidepressant-like responses. The molecular mechanisms underlying ketamine's antidepressant responses are shown in Figure 1.

Importantly, almost 20 years after the groundbreaking discovery that ketamine effectively produces rapid and sustained antidepressant effects, particularly in March 2019, the United States Food and Drug Administration approved the use of (S)-ketamine nasal spray (Spravato™) for treatment-resistant MDD. In the same year, (S)-ketamine nasal spray was approved for use in treatment-resistant depression in Europe[21]. Despite the fast and long-lasting antidepressant effects of ketamine, there is much concern about its abuse potential and serious adverse effects[9]. For this reason, ketamine is only available through a restricted distribution system, limiting its widespread clinical use. Although there are some drawbacks associated with its use, it may serve as a prototype for screening novel fast antidepressant agents. Given this scenario, the search for ketamine-like compounds has emerged as a promising therapeutic strategy. In this regard, our research group and others have shown that agmatine is also able to produce fast antidepressant responses and shares some mechanisms of action with ketamine[10].

AGMATINE AS A NOVEL CANDIDATE FOR FAST ANTIDEPRESSANT RESPONSES

Agmatine, a cationic amine produced from the L-arginine in a reaction catalyzed by the enzyme arginine decarboxylase, is widely distributed in human tissues, including the brain[22-24]. For almost a century, it was wrongly believed that agmatine was produced by bacteria, plants, and fish but not mammals[25]. Agmatine was "rediscovered" in 1994 during the search for an endogenous ligand for imidazoline binding sites[24]. In this study, a molecule was isolated from the mammalian brain and identified as agmatine[24]. This was the starting point for many studies that have evaluated the biological properties and possible beneficial effects of agmatine on a wide variety of diseases[26].

Soon after providing evidence of the presence of agmatine in mammalian nervous tissue, Piletz *et al*[27] documented its neuroprotective effects. The neuroprotective effects of agmatine reportedly involve protection mechanisms against excitotoxicity, since agmatine may block NMDA receptors and inhibit the increase in intracellular calcium concentrations in different neuronal cell cultures[28-30]. The NMDA receptor

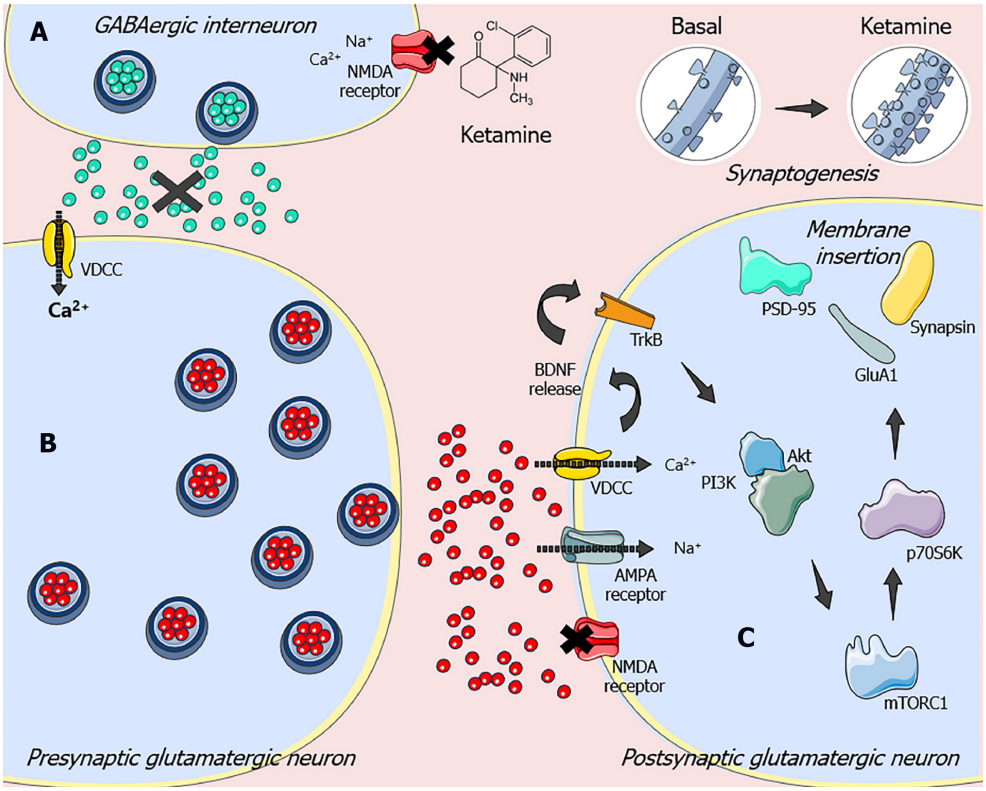


Figure 1 Supposed intracellular signaling pathway implicated in ketamine's antidepressant-like effects. A: Ketamine antagonizes N-methyl-D-aspartic acid receptors in GABAergic interneurons, which in turn attenuate the inhibitory action of this system on glutamatergic tonus. Subsequently, the disinhibition of pyramidal cells results in a burst of glutamatergic transmission; B: The glutamate released in the synaptic cleft preferentially stimulates alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid (AMPA) receptors, which promotes a transient sodium influx that depolarizes the neurons and activates voltage-dependent calcium channels. C: This event causes the exocytosis of synaptic vesicles containing brain-derived neurotrophic factor (BDNF) in the synaptic cleft[16,122]. BDNF culminates in protein kinase B activation that can phosphorylate and activate mechanistic target of rapamycin complex 1 (mTORC1). In turn, mTORC1 phosphorylates the 70-kDa ribosomal protein S6 kinase at Thr389, which regulates synaptic protein synthesis such as AMPA receptor subunit 1 and postsynaptic density-95, which contribute to dendritic spine formation and synaptogenesis[17,13]. NMDA: N-methyl-D-aspartic acid; AMPA: Alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid; BDNF: Brain-derived neurotrophic factor; VDCC: Voltage-dependent calcium channels; PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; TrkB: Tropomyosin receptor kinase B; GluA1: Glutamate AMPA receptor subunit 1; mTORC1: mechanistic target of rapamycin complex 1; PSD-95: postsynaptic density protein-95 kDa.

is an ion channel controlled by glutamatergic excitation, which is essential for the normal functioning of the central nervous system (CNS), including cognitive function, locomotion, and breathing[31-33]. This type of receptor is located on the membranes of neuronal and glial cells[34], and is implicated in the development and maintenance of acute and chronic diseases of the CNS, such as stroke, Parkinson's disease, Alzheimer's disease, MDD, and schizophrenia[34]. Under excitotoxic conditions, the increase in extracellular glutamate intensifies NMDA receptor activation, causing an influx of Ca^{2+} and Na^{+}[34]. NMDA receptor stimulation also activates nitric oxide (NO) production pathways by activating nitric oxide synthase, thereby generating NO, one of the main mediators of cellular death[35,36]. The inhibition of NO synthesis is potentially beneficial in the treatment of brain disorders associated with its overproduction. Several studies have shown that the neuroprotective properties of agmatine in several neurodegenerative diseases are related to its ability to antagonize NMDA receptors and inhibit NO synthesis as well as its potential to counteract the effects of oxidative stress[37].

The first evidence of the antidepressant effects of agmatine was reported in a study that examined its impact on behavioral tests related to depression (immobility time in the tail suspension test and forced swimming test) in mice[38]. Since then, other studies have confirmed the antidepressant efficacy of agmatine in behavioral tests in rodents[39-41]. Subsequent studies implicated several molecular targets in the antidepressant effect of agmatine, namely the modulation of: (1) K^{+} channels[42]; (2) NO synthesis[43,44]; and (3) several neurotransmitter receptors including NMDA receptors[38,45], AMPA receptors[46,47], GABA receptors[48], serotonin receptors[49,50], and opioid system receptors[51].

In 2010, a human clinical trial showed the safety of oral agmatine[52]. In 2013, Shopsin *et al*[53] provided the first evidence that agmatine may effectively treat MDD, but this study included only three patients. None of these three patients treated with agmatine relapsed after the joint administration of a serotonin-depleting drug, indicating that the mechanism underlying the antidepressant action of agmatine is likely unrelated to the serotonergic system[53]. It was also reported that 8-wk treatment with the standard antidepressant bupropion normalized plasma agmatine levels[54]. In brain autopsies of chronically depressed patients, Bernstein *et al*[55] reported a significant increase in agmatinase immunoreactivity in hippocampal neurons, suggesting the role of the agmatinergic system in MDD pathophysiology. However, it was not possible to determine the exact reason why levels of this enzyme increased in hippocampal neurons due to the use of antidepressants.

In 2018, a gas chromatography–mass spectrometry study quantified agmatine levels in the brains of post-mortem humans who died by suicide and showed reduced agmatine levels in the suicide cortex regardless of these individuals formerly meeting the criteria for MDD versus controls[56].

Weiss *et al*[57] presented evidence of the activity of the agmatinergic system in habenular nuclei and investigated the actions of agmatine and agmatinase in the rat and human habenular systems. It is important to highlight that the role of habenular nuclei in mental disorders, including MDD, has already been considered[58,59]. In this study, agmatine was demonstrated responsible for the strong decrease in the spontaneous action potential of medial habenular neurons by activating type I1 imidazoline receptors. It was also reported that increased activity of the agmatinergic system in habenular nuclei may strengthen the dopaminergic activity of the midbrain. This evidence suggests dysregulation in the habenular-interpeduncular axis in patients with MDD[57].

In summary, these results present the possible role of agmatine in the neurobiology of MDD and highlight the possible benefits of agmatine as antidepressant therapy.

Recent evidence has also demonstrated the possible fast antidepressant-like actions of agmatine (Figure 2)[10]. In this context, Neis *et al*[46] reported that the antidepressant-like effect of agmatine administered orally to mice subjected to the tail suspension test is dependent on the modulation of molecular targets associated with the fast antidepressant-like effect displayed by ketamine. In particular, the antidepressant-like effect elicited by the acute administration of agmatine in the tail suspension test appears to involve inhibition of NMDA receptors since it enhanced the antidepressant potency of MK-801 (an NMDA receptor antagonist) up to 100-fold[60]. Moreover, the antidepressant-like effect of agmatine in the tail suspension test is dependent on AMPA and TrkB receptor activation since the administration of 6,7-dinitroquinoxaline-2,3-dione (DNQX; an AMPA receptor antagonist) or K-252a (a TrkB receptor antagonist) completely abolished its antidepressant-like response[46]. A single dose of agmatine also increased BDNF levels in the prefrontal cortex of mice, and its antidepressant-like effect in the tail suspension test was abrogated by the administration of anti-BDNF antibody. Of note, the antidepressant-like effect of agmatine is also dependent on PI3K/Akt/glycogen synthase kinase-**3**β (GSK-3β)/ mTOR signaling. In particular, the administration of LY294002 (a PI3K inhibitor) or rapamycin (a selective mTOR inhibitor) completely abrogated the behavioral responses of agmatine in the tail suspension test. Combined treatment with a sub-effective dose of agmatine and lithium chloride (a non-selective GSK-3β inhibitor) or AR-A014418 (a selective GSK-3β inhibitor) produced an antidepressant-like effect in the tail suspension test[46]. Importantly, these behavioral responses were accompanied by an increase in BDNF, GluA1, and PSD-95 immunocontent in the prefrontal cortex of mice[46].

Supporting the assumption that agmatine could elicit a fast antidepressant-like effect, a study by Neis *et al*[61] demonstrated that a single dose of agmatine effectively reversed the depressive-like behavior induced by chronic unpredictable stress. In this study, mice were exposed to the stress protocol for 14 d and received a single oral dose of agmatine, ketamine, or fluoxetine. The results indicated that a single dose of agmatine or ketamine (after 24 h), but not fluoxetine, counteracted the depressive-like behavior induced by the stress protocol in the tail suspension test[61].

Expanding upon these findings, Neis *et al*[62] reinforced the ability of agmatine to rapidly reverse the depressive-like behavior induced by the 21-d administration of corticosterone, a pharmacological model of stress in mice. In the tail suspension test, a single dose of agmatine or ketamine abolished the depressive-like behavior of mice chronically exposed to corticosterone. In addition, treatment increased GluA1 immunocontent in the hippocampus of control animals[62]. Notably, a single dose of fluoxetine did not produce the same effects as ketamine or agmatine[62]. Chronic

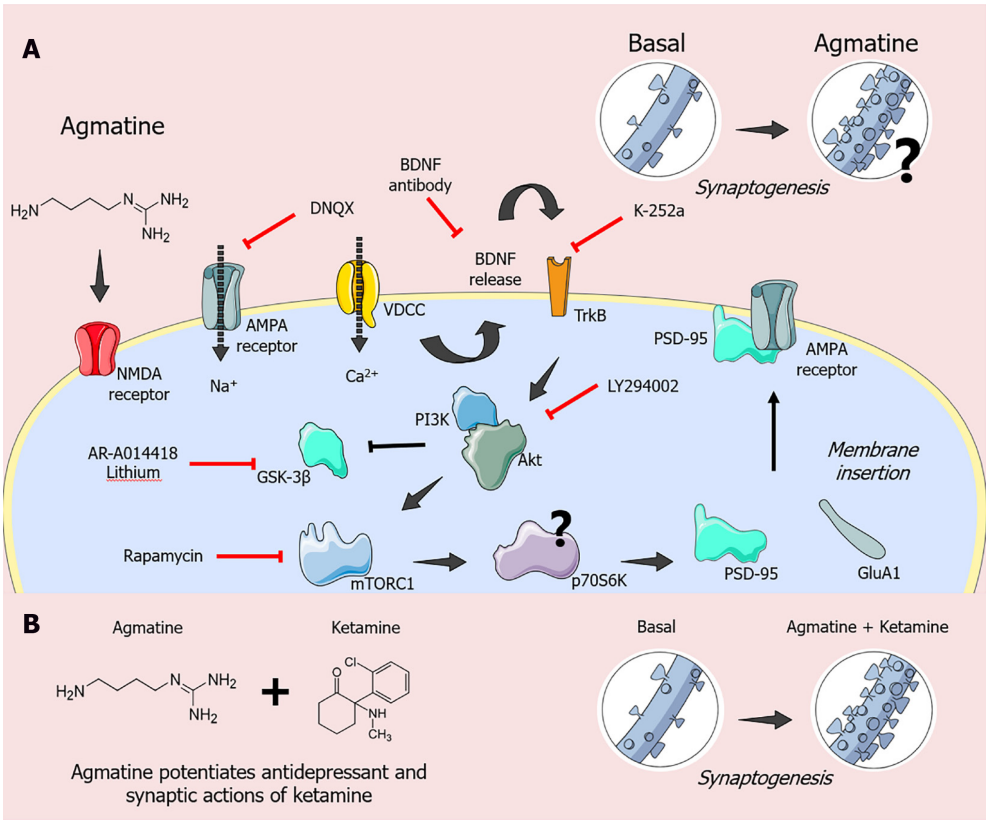


Figure 2 Putative signaling pathways implicated in the rapid-acting antidepressant-like effects of agmatine. A: The antidepressant-like effect elicited by the acute administration of agmatine in the tail suspension test appears to involve inhibition of N-methyl-D-aspartic acid (NMDA) receptors since it enhanced the antidepressant potency of MK-801 (an NMDA receptor antagonist) by up to 100-fold[60]. Moreover, agmatine's antidepressant-like effect in the tail suspension test is dependent on the activation of alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid (AMPA) and tropomyosin receptor kinase B (TrkB) receptors since the administration of 6,7-dinitroquinoxaline-2,3-dione (DNQX; an AMPA receptor antagonist) or K-252a (a TrkB receptor antagonist) completely abolished its antidepressant-like response. The antibody anti-brain-derived neurotrophic factor (BDNF) also abolished the antidepressant-like effect elicited by agmatine in the tail suspension test[46]. Of note, the antidepressant-like effect of agmatine is also dependent on phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/ glycogen synthase kinase-3β/mechanistic target of rapamycin (mTOR) signaling. In particular, the administration of LY294002 (a PI3K inhibitor) or rapamycin (a selective mTOR inhibitor) completely abrogated the behavioral responses of agmatine in the tail suspension test. The combined treatment with a sub-effective dose of agmatine and lithium chloride (10 mg/kg, po; a non-selective GSK-3β inhibitor) or AR-A014418 (a selective GSK-3β inhibitor) produced an antidepressant-like effect in the tail suspension test[46]. Importantly, these behavioral responses were accompanied by an increase in the BDNF, glutamate AMPA receptor subunit 1 and postsynaptic density protein-95 kDa immunocontent in the prefrontal cortex of the mice[46]; B: Reinforcing the notion that ketamine and agmatine share common behavioral responses and molecular targets, the ability of agmatine to potentiate the antidepressant and synaptic actions of ketamine was also demonstrated[47]. In particular, the combined administration of subthreshold doses of agmatine and ketamine produced a fast (starting in 1 h) and sustained (lasting up to 7 d) antidepressant-like effect in the tail suspension test. These behavioral responses were associated with stimulation of the Akt/70-kDa ribosomal protein S6 kinase signaling pathway and increased synaptic protein synthesis in the prefrontal cortex in a time-dependent manner. More importantly, the combined administration of sub-effective doses of agmatine and ketamine raised the dendritic arbor and spine densities and effectively remodeled the dendritic spinal architecture in the prefrontal cortex[47]. NMDA: N-methyl-D-aspartic acid; AMPA: Alpha-amino-3-hydroxy-methyl-5-4-isoxazole propionic acid; BDNF: Brain-derived neurotrophic factor; VDCC: Voltage-dependent calcium channels; PI3K: Phosphatidylinositol 3-kinase; Akt: Protein kinase B; TrkB: Tropomyosin receptor kinase B; GluA1: Glutamate AMPA receptor subunit 1; mTORC1: mechanistic target of rapamycin complex 1; PSD-95: postsynaptic density protein-95 kDa; GSK-3β: Glycogen synthase kinase-3 β.

unpredictable stress and chronic corticosterone administration models are sensitive to chronic but not acute administration of conventional antidepressants, but a single dose of ketamine sufficiently produced antidepressant responses in these models[62]. Moreover, a single dose of agmatine or ketamine counteracted the depressive-like phenotype of cAMP-responsive element binding protein–regulated transcription coactivator 1 knockout mice in the forced swimming test, reinforcing the notion that agmatine could have a rapid antidepressant-like effect[63].

Subsequent studies provided novel evidence that a low-dose combination of ketamine plus agmatine produced neuroprotective, antidepressant-like, and synaptogenic effects[11,64,65]. A study using the HT-22 mouse hippocampal neuronal cell line reported that the combined use of sub-effective concentrations of ketamine and agmatine prevented the neuronal damage caused by corticosterone[64]. Of note, this effect was associated with increased phosphorylation of Akt (Ser^{473}), p70S6K (Thr^{389}), and PSD-95 immunocontent[65]. These data support the idea that ketamine

and agmatine share common molecular targets and could work in tandem to protect neuronal cells from the harmful effects of corticosterone by activating Akt/mTORC1/p70S6K signaling, resulting in synaptic protein expression[11,65].

Reinforcing these findings, Freitas *et al*[47] investigated the ability of agmatine to potentiate the effects of the antidepressant and synaptic actions of ketamine in mice. Of special interest, the combination of single subthreshold doses of ketamine and agmatine exerted antidepressant-like and pro-synaptogenic actions in a time-dependent manner. In particular, agmatine plus ketamine produced fast (1 and 24 h) and sustained (7-d) antidepressant-like effects in the tail suspension test[47]. Furthermore, this combined treatment increased p70S6K phosphorylation and GluA1 immunocontent in the prefrontal cortex 1 h after treatment. This same protocol increased the PSD-95 immunocontent, an effect that persisted for up to 7 d. The combined treatment also increased the complexity of the dendritic branches after 24 h, and this effect lasted up to 7 d. Likewise, ketamine plus agmatine treatment effectively increased the dendritic spinal density after 1 h later, a response that lasted up to 24 h [47]. These results reinforce the notion that agmatine and ketamine share common molecular targets and expand the findings regarding the ability of agmatine to enhance the antidepressant-like and synaptic actions of ketamine[47].

Taken together, these results support the hypothesis that agmatine can act as a ketamine-like compound, and further studies are crucial to investigate whether the rapid antidepressant effects of agmatine are reproducible in patients with MDD. Moreover, the use of agmatine in the clinic would be highly promising owing to its safety, even at high doses, without evident effects of toxicity[26,52].

BEYOND mTORC1 HYPOTHESIS

In addition to focusing on the importance of the mTORC1-mediated signaling pathway for the antidepressant effect of agmatine, some studies investigated other signaling pathways that may play a role in its antidepressant effect. Understanding other pathways influenced by agmatine is important to its establishment as a therapeutic alternative in the clinical setting.

Regarding the factors that may influence the mechanisms associated with MDD symptoms, neuroinflammation has received much attention in recent years. Neuroinflammation reportedly plays an essential role in several neuropathologies, such as multiple sclerosis, Alzheimer's disease, and MDD[66,67]. It was demonstrated in both humans and animals that immunological challenges may induce depressive behavior [68]. It is important to note that, since the 1990s, several studies reported a strong correlation between MDD and peripheral inflammatory markers[69,70].

In the last few years, three meta-analyses aimed to better understand the relationship between neuroinflammation and the development/maintenance of MDD. Kappelmann *et al*[71] published a meta-analysis in 2018 that analyzed data from four randomized controlled studies that examined the effects of pro-inflammatory cytokine inhibitors. In these studies, adalimumab and etanercept were used, and both treatments improved depressive symptoms in patients. In 2019, a randomized clinical study showed more pronounced antidepressant results in patients with higher high-sensitivity C-reactive protein levels[72]. In this study, the use of anti-inflammatory drugs improved clinical signs of depression, such as motor retardation, suicidal thoughts, and depressed mood[72]. Another meta-analysis evaluated 36 studies and assessed the effects of anti-inflammatory drugs in almost 10000 patients[73]. The findings suggested that the use of anti-inflammatory drugs sufficiently reversed depressive symptoms. The latest meta-analysis combined 26 randomized clinical trials of over 1500 patients[74]. This study also verified the improvement in depressive symptoms in patients with anti-inflammatory agent use[74].

Therefore, inflammatory pathways play an important role in the development and maintenance of depressive symptoms. Increasing evidence has shown that agmatine also acts on neuroinflammatory-related pathways that may participate in rapid-onset antidepressant responses.

The early administration of agmatine for 7 d prevented the depressive-like behavior caused by lipopolysaccharide (LPS) challenge in mice[75]. Agmatine pretreatment counteracted LPS-induced neuroinflammation by preventing increases in interleukin (IL)-1β and tumor necrosis factor (TNF)-α level in the murine brain. In addition, agmatine positively regulates BDNF levels in the hippocampus[75]. In another study, agmatine pretreatment also normalized LPS-induced sickness behavior in rats in addition to decreasing serum concentrations of IL-6 and TNF-α[76]. Zarifkar *et al*[77]

reported that agmatine prevented LPS-induced spatial memory impairment and hippocampal caspase-3 activation in LPS-treated rats. It is also noteworthy that agmatine effectively inhibited the LPS-induced production of nitrite and decreased body temperature in rats in a dose-dependent manner[78].

Notably, Neis *et al*[45] showed that agmatine effectively counteracted the depressive-like behavior induced by the pro-inflammatory cytokine TNF-α in mice. In this study, the combined treatment of sub-effective doses of agmatine and fluoxetine, imipramine, bupropion, MK-801, or 7-nitroindazole resulted in a synergistic antidepressant-like effect in mice subjected to TNF-α administration[45].

Agmatine also exhibits anti-inflammatory effects in other disease models. In particular, in a type 2 diabetes mellitus (T2DM) model induced by a high-fat diet for 12 wk, anxiety- and depressive-like behaviors were associated with an increase in pro-inflammatory cytokines, such as IL-6 and TNF-α, as well as a decrease in the BDNF immunocontent in the rat hippocampus[79]. These parameters were inhibited by agmatine treatment in the last 4 wk of the protocol. In this study, agmatine levels in the hippocampus of rats subjected to the T2DM protocol were significantly lower than those in the control animals[79].

In an Alzheimer's disease model, the administration of amyloid-β peptide ($A\beta_{1-42}$) to mice caused depressive-like behavior in the forced swimming test, an effect parallel to an increase in the pro-inflammatory cytokines IL-6 and TNF-α in the hippocampus [80]. Both depressive-like behavior and pro-inflammatory markers were reversed by agmatine treatment, suggesting that the anti-inflammatory properties of agmatine may be related to its antidepressant effect. Notably, this study also detected lower concentrations of agmatine in the brains of animals injected with $A\beta_{1-42}$[80]. These data point to the action of agmatine in neuroinflammatory processes, as a pharmacological strategy to decrease depressive-like behavior, including that associated with comorbid diseases, such as T2DM and Alzheimer's disease.

It is important to note that the activation of various types of inflammasomes is a critical target in the inflammatory response. Inflammasomes are involved in the development of several neurological diseases, including MDD[81,82]. Among them, the NLR family pyrin domain containing 3 (NLRP3) inflammasome is the most closely related to MDD due to the exaggerated activation of inflammatory and immunological responses that contribute to the pathogenesis and progression of this disorder[83]. A compelling study reported that depressive-like behavior in mice subjected to LPS administration is related to NLRP3-dependent caspase-1 activation[84]. Accordingly, anxiety-like behavior reportedly occurs in rats exposed to neonatal inflammation or inflammatory stress early in life triggered by NLRP3 inflammasome activation in animals' brains[85]. Altogether, evidence suggests that the NLRP3 inflammasome plays an essential role in the neurobiology of MDD and may be a potential target for antidepressant treatment.

In this regard, ketamine was shown to exert an antidepressant effect in the LPS-induced model *via* suppressing the NLRP3 inflammasome and upregulating AMPA receptors[86]. Importantly, in this study, the authors postulated that ketamine might increase AMPA receptor expression through the NLRP3 inflammasome, suggesting that NLRP3 could be a target in fast-acting antidepressant treatment[86].

The possibility that agmatine exerts antidepressant effects by modulating neuroinflammatory mechanisms has also been investigated. Sahin *et al*[43] investigated the effects of agmatine in a model of restraint stress–induced depressive-like behavior. The authors demonstrated that agmatine rescued anti-inflammatory cytokine IL-4 and IL-10 levels that were impaired by stress[43]. Moreover, the 6-wk treatment with agmatine counteracted the depressive-like behavior of animals exposed to chronic unpredictable stress by suppressing NLRP3 and IL-1β[43].

The exact role of the NLRP3 inflammasome–driven signaling pathway in MDD pathophysiology and antidepressant responses is still not well established. However, it has been proposed that the gut microbiota may influence activation of the NLRP3 inflammasome and neuroinflammatory processes through the microbiota-gut-brain axis.

The microbiome, a complex ecosystem in the human gut, includes bacteria, viruses, archaea, and fungi. The bacteria present in this system regulate aspects of the host's health, mainly brain development and functioning[87,88]. The microbiome is a dynamic structure that is affected by delivery type, sex, age, nutrition, stress, and medications[89]. These interferences can compromise the balance between pathogenic and commensal bacteria[90], promoting the development of a process called dysbiosis, which can change the permeability of the intestinal wall, allowing bacteria and their products to leak into the sterile cavity and activate the immune response[91]. Immune response activation increases the levels of pro-inflammatory cytokines, which, together

with other toxic metabolites, damage the blood–brain barrier and trigger neuroinflammation[92].

The immune and brain mechanisms involved in intestinal dysbiosis may include microglial activation[93]. Microglia are responsible for releasing pro-inflammatory cytokines in the brain when activated by stress, a mechanism that is altered in MDD [94,95]. On the other hand, a balanced and healthy microbiota can regulate the activation of these stress response pathways through the synthesis of hormones and neurotransmitters, minimizing the effects of such stressors[96].

Studies have shown that there is a "microbiota of MDD" due to the difference in composition between depressed patients and healthy controls. In a microbiome study of patients with MDD and irritable bowel syndrome, less bacterial diversity, an effect associated with increased levels of bacteria from the phylum Bacteroidetes, and increased colon inflammation were noted in patients compared to healthy controls [97]. In a Chinese cohort, the microbiota of patients with MDD showed higher concentration of Proteobacteria and decreased concentrations of Firmicutes[98].

Several studies have suggested the direct modulation of bacteria in the immune system. *Proteo mirabilis*, a proteobacterium, can activate the NLRP3 inflammasome and interleukin IL-1b production[99]. Other components of Proteobacteria, such as the LPS produced by *Pseudomonas*, are related to the development of MDD symptoms *via* activation of the NLRP3 inflammasome and pro-inflammatory immunoglobulins[93]. In patients with MDD, an increase in some Bacteroidetes species (*Parabacteroidetes* and *Alistepes*) reportedly converts tryptophan to indole, which can influence the availability of tryptophan in the body and affect serotonergic balance[100]. Other studies confirmed an increase in *Alistepes* bacteria in patients with MDD, chronic fatigue syndrome, irritable bowel syndrome, and stress models[101,102].

The transplantation of fecal microbiota from patients diagnosed with MDD to germ-free microbiota mice triggered anxious-, anhedonic-, and depressive-like behaviors in the animals[103,104]. This evidence suggests that the depressive phenotype may be transmitted by gut microbiota. These data show a close relationship between the composition of the gut microbiota and brain health, mainly in the pathological mechanisms involved in the development and maintenance of depressive symptoms. Furthermore, the immune system/NLRP3 inflammasome acts as an intermediary between gut dysbiosis and brain function.

Some studies have suggested that the ability of ketamine to elicit antidepressant effects may be mediated, at least in part, by modulation of the microbiota-gut-brain axis. Two studies that investigated the effects of ketamine administration in the gut microbiota of mice following the social defeat stress model reported that the treatment attenuated the alterations in *Bacteroidales*, *Clostridiales*, *Ruminococcaceae*, *Deltaproteobacteria*, and *Mollicutes* bacterial levels in their feces[105,106]. Moreover, ketamine prevented the increase in the *Clostridium* and *Butyricimonas* species induced by the stress model[105,106]. Other studies showed that ketamine significantly amplified the number of healthy bacteria and decreased the number of opportunistic pathogens in Wistar rats[107]. In an inflammatory model of LPS-induced depressive-like behavior, ketamine improved the diversity of the gut microbiota, positively regulating this microsystem[108]. Together, these data suggest that ketamine influences the composition of the microbiota, a response that may underlie its antidepressant-like effects.

The relationship between gut microbiota and agmatine levels has emerged and may play a role in the ability of gut microbiota to influence mental health. Agmatine is produced and released by gut bacteria of the human microbiome[109] and can be obtained from ingested food[110,111]. The composition of the intestinal microbiota influences agmatine availability in the gut lumen for absorption, and the majority of agmatine in humans is believed to be derived from bacterial sources[27]. Interestingly, agmatine may also be obtained from foodstuffs, particularly fermented foods such as alcoholic beverages (wine, beer, sake), which suggests the role of yeast in its production[109]. The filamentous fungus *Aspergillus oryzae*, which is widely used for the production of various Asian fermented foods, can enhance agmatine ingestion [112].

The consumption of fermented foods has beneficial effects on mental health[113]. The use of probiotics also reportedly exerts positive effects on depressive symptoms [114,115]. The possibility that agmatine is produced in the gut following the consumption of fermented foods and probiotics may account, at least in part, for its anti-inflammatory and antidepressant effects should be investigated in future studies.

Metformin, the mainstay therapy for T2DM, reportedly influences the diversity and composition of the gut microbiota[116]. This drug has recently been shown to act on *Escherichia coli*, elevating agmatine production and increases the longevity of

Caenorhabditis elegans[117]. Metformin has been shown to produce antidepressant effects in depressed patients with diabetes mellitus[118] and proposed as an adjunctive antidepressant approach in nondiabetic patients with MDD[119]. It remains to be determined whether agmatine levels are higher in individuals taking metformin and, if so, whether it contributes to the antidepressant effect observed with metformin treatment.

CONCLUSION

Agmatine, an endogenous cationic amine, exerted antidepressant effects in several preclinical studies[26,120]. Considering that the microbiota composition and consumption of fermented foods, or even some drugs such as metformin, may influence agmatine levels in the gut[27,109-119], it remains to be established whether agmatine derived from these sources may positively impact mood and exert antidepressant effects. Therefore, modulation of the microbiota and, consequently, gut agmatine levels may represent a novel approach to mood regulation.

In addition to the fact that agmatine may be synthesized by gut microbiota, several studies have indicated that it is safe even when administered at high doses as a nutraceutical. The sulfate salt of agmatine has been used for bodybuilding[27] and the management of neuropathic pain at doses as high as 2.6 g/day[121]. The fact that agmatine also exhibits several beneficial effects for a wide spectrum of diseases[27] suggests that it is a promising therapeutic strategy for the management of MDD and several comorbid diseases and inflammatory clinical conditions such as diabetes, obesity, pain, and neurodegenerative diseases. Of particular relevance, compelling preclinical evidence has indicated that agmatine has the ability to counteract several neuroinflammatory markers induced by models of depression and shares with ketamine the ability to elicit fast antidepressant responses[46,47,61,62,75-80]. The possibility that agmatine may afford a rapid antidepressant effect would give it an advantage over conventional antidepressants that require several weeks to alleviate depressive symptoms. In preclinical studies, agmatine elicited a synergistic effect with ketamine in mice subjected to animal models of depression as well as cell culture, and pharmacological evidence has pointed to similar molecular mechanisms of these drugs [46]. These properties of agmatine clearly warrant future clinical investigation of its beneficial effects for managing depressive symptoms as a monotherapy or adjunctive treatment. Therefore, clinical studies are warranted that investigate the possibility that agmatine may be combined with low doses of ketamine to diminish the side effects and provide synergistic antidepressant effects.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 997-1016

DOI: 10.5498/wjp.v11.i11.997

ISSN 2220-3206 (online)

REVIEW

Healthy diet, depression and quality of life: A narrative review of biological mechanisms and primary prevention opportunities

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Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country/Territory of origin: Spain

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

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Abstract

Unipolar depressive disorder (UDD) affects more than 264 million people worldwide and was projected well before the severe acute respiratory syndrome coronavirus 2 pandemic to be the leading cause of disability-adjusted life years

Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Received: February 27, 2021
Peer-review started: February 27, 2021
First decision: June 5, 2021
Revised: June 19, 2021
Accepted: August 27, 2021
Article in press: August 27, 2021
Published online: November 19, 2021

P-Reviewer: Socea B, Tu WJ
S-Editor: Ma YJ
L-Editor: A
P-Editor: Yu HG

lost in 2030. It is imperative for leading economies to implement preventive strategies targeted towards UDD, given consistent policies are currently lacking. Recently established similarities between the aetiological hypotheses of depression and cardiometabolic diseases are shifting paradigms within this field. It is believed that dietary practices could potentially reduce the incidence of depression; similar to their effects on metabolism. Thus, the aim of this review was to compile current evidence on healthy dietary patterns as suitable contributors towards primary prevention strategies against UDD. Most of the well-known biological mechanisms behind depression have been positively associated with healthful diets and dietary patterns to varying degrees. Interestingly, a common factor of UDD is the production and overall effects of inflammatory cytokines, such as interleukin-6, tumor necrosis factor-α, and C-reactive protein. These compounds have been associated with depressive symptoms, disturbances in neuroendocrine function, leaky gut, monoamine activity and brain function, while also being key factors in the development of cardiometabolic diseases. The Mediterranean diet (MD) in particular, is well supported by first-level evidence regarding its preventive qualities against metabolic and cardiovascular diseases and thus considered a model for healthy eating by various organizations. In one of the few clinical trials investigating these associations, the PREDIMED trial, individuals with diabetes assigned to a MD supplemented with mixed tree nuts experienced a 41% relative risk reduction for developing depression. Lastly, there is a need to include health related quality of life as an indicator of physical and mental well-being, considering its putative associations with depression and suicide risk. Going forward, focusing on clinical trials, using precise nutritional assessments, and identifying nutritional biomarkers which may be related to depression are needed to fully support the implementation of dietary recommendations in the field of psychiatry.

Key Words: Depression; Nutrition; Mediterranean; Quality of life; Primary prevention; Epidemiology

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Core Tip: Parallel biological mechanisms are being uncovered that link both depression and cardiometabolic diseases. Based on this evidence, it has been theorized that a healthful diet could improve the prognosis and prevent depression incidence, similar to its effects on cardiovascular risk. Current epidemiological studies support the link between healthy diets and better symptom management, biomarkers, and health related quality of life related to depression. However, additional longitudinal studies and dedicated clinical trials are needed to fully understand these initial findings. With greater evidence, healthy dietary patterns, such as the Mediterranean diet, could facilitate the management and reduce the risk of depression.

Citation: Pano O, Martínez-Lapiscina EH, Sayón-Orea C, Martinez-Gonzalez MA, Martinez JA, Sanchez-Villegas A. Healthy diet, depression and quality of life: A narrative review of biological mechanisms and primary prevention opportunities. *World J Psychiatr* 2021; 11(11): 997-1016
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/997.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.997

INTRODUCTION

More than 264 million people suffer from unipolar depressive disorder (UDD) worldwide, making it a leading cause of years of life lost as a result of disability[1]. In 2019, unipolar depressive disorder was ranked in 6th place amongst the top causes of burden of disease for the age groups between 25-49 years[2]. Previous projections had already speculated that depressive disorders would be the leading cause of disability-adjusted life years lost by the year 2030[3]. These estimations will inevitably rise as a

result of the COVID-19 pandemic, requiring the implementation of public health policies to contain this expansive global health issue[4].

Current efforts to prevent mental illness, including depression focus on early diagnosis with prompt medical attention and treatment, in addition to sufficient drug availability[5]; in other words, secondary prevention. Despite moderate success in some countries, current research is offering both a better understanding of this condition and the rationale to apply new preventive strategies based on this knowledge. Examples of such research have been carried out by Sanchez-Villegas *et al* [6,7] in a population of southern Europeans. In this study sample, poor dietary and sedentary behaviors were associated with a higher incidence of mental illnesses (including UDD), which are also determinants typically associated with cardiometabolic health[8]. Due to common biological pathways, nutritional epidemiology now offers further insights in the field of mental illnesses[9].

Regardless of promising reports which support the possibility of improving mental health through nutrition, evidence remains limited[10]. Some of the findings refer to the importance of maternal and early-life nutrition for prevention, but also the role of diet as a determinant of adequate symptom management and enhanced antidepressant drug efficacy. Such findings have led to an exponential growth and interest in the prevention of UDD through primary prevention strategies[11-13]. Nonetheless, the implementation of such strategies requires solid, reproducible evidence which can only be obtained from nutritional intervention trials.

In this narrative review we summarize the available evidence on the biological mechanisms common to UDD and cardiometabolic diseases, in support of the implementation of dietary interventions as plausible preventive measures for these diseases. For this purpose, we provide an overview of the aetiological hypotheses of depression with a particular interest in the role of diet on these pathways. Finally, current epidemiological evidence on the best known healthful dietary pattern, the Mediterranean diet (MD), will be presented in support of dietary interventions to reduce depression incidence and aid overall prognosis.

AETIOLOGICAL HYPOTHESES OF DEPRESSION

A wide array of determinants are involved in the aetiology of depression, including biological, psychological, and environmental factors[5]. It is not unlikely that these mechanisms coexist in varying degrees with plausible synergistic activity; adding complexity and variability to the causes and clinical manifestation of UDD. Among the most accepted pathways is the dysregulation of hormonal signaling involving the Hypothalamus-Pituitary-Adrenal (HPA) axis, although monoamine activity, neurogenesis, neuronal activity and plasticity play fundamental roles in the aetiology of mental illnesses in general. Of note, oxidative stress and inflammation play a common role in most of these hypotheses[14].

Oxidative stress and pro-inflammatory state

Most of the associated biological mechanisms in depressive disorders are accompanied by the production and release of cytokines, such as interleukin (IL)-1b, IL-2, IL-6, interferon-γ (INT-γ) and tumor necrosis factor (TNF)-α. These disturbances have been confirmed in patients with UDD, among whom plasma levels of certain pro-inflammatory cytokines (TNF-α, IL-6, IL-8, and C-reactive protein among others) are significantly higher than those of healthy individuals[15-17]. Furthermore, effective pharmacological treatment decrease cytokine concentrations, particularly IL-6, C-reactive protein and INT-γ[17,18]. The basis for this aetiological hypothesis is the damage to the blood brain barrier (BBB) caused by the convergence of oxidative stress and pro-inflammatory signals, which impede an adequate brain function[19]. These alterations are particularly noticeable in the BBB tight junction protein, claudin 5 (Cldn5), increasing cytokine permeability to the brain of mice[19,20]. Additionally, altered BBB function promotes the infiltration of various immune cells into the brain, endothelial damage through *hdac1* expression, and direct damage to astrocytes, glial cells, and neurons[5,21,22]. Further release of peripheral cytokines originate in tissues such as the adipose tissue and gastrointestinal tract, resulting in vagal nerve stimulation, which also reinforces this pro-inflammatory state[19,23]. Each of these signals converge in the central nervous system (CNS) and result in altered receptor expression, neurogenesis and plasticity[5,19].

Given these connections, inflammatory cytokines have been proposed as biomarkers for depression in association with cardiovascular disease. These markers

span various biological levels, including single-nucleotide polymorphisms identified in genome wide analyses, but also molecules such as the neutrophil gelatinase associated lipocalin[24]. Of particular interest are the associations found between the loci coding for the pro-inflammatory cytokine IL-6 and antidepressant responsiveness [25]. Oxidative stress and inflammation are also directly correlated to indoleamine 2,3-dioxygenase (a rate limiting enzyme in the metabolism of tryptophan), which leads to neurotoxicity and serotonin deficiency in the brain; both core features of the pathophysiology of depression[26].

These results are of great interest as UDD can be thought of as an inflammation-based disease, but also indicate potential anti-oxidant properties exerted by anti-depressant drug therapies. Overall, these findings offer new preventive strategies to the field of mood disorders. Regarding the robustness of these findings, a 2015 cumulative meta-analysis analyzing 58 studies evidenced that the role of the most commonly associated inflammatory cytokines on UDD was substantial[16]. Additionally, these results explain the diversity of clinical manifestations and responsiveness to treatment as a result of the interplay between biological pathways and individual factors. In this regard, we cannot disregard the potential effect of confounding as a plausible explanation for these differences, given the lack of clinical trials controlling for the numerous determinants of UDD.

Hypothalamus-pituitary-adrenal axis

Well-defined clinical and biochemical evidence support the role of glucocorticoid dysregulation as a cause of depression. The release of cortisol is the end product of the HPA-axis in response to external stress[5]. Moreover, circulating cortisol levels activate the sympathetic nervous system, and other immune responses that influence neuronal activity. Despite this being a natural response, disparities have been found in both animal and human models revealing individualized responses to external stressors, and thus differences in UDD risk[27]. With regard to this hypothesis of UDD, sustained induced stress will lead to the down regulation of glucocorticoid receptors in the CNS. Normally, cortisol inhibits the further release of corticotropin-releasing hormone and adrenocorticotrophic hormone in a self-regulating cycle. However, this negative feedback is altered in patients with depression, leading to sustained elevated levels of cortisol, alterations of the cortisol circadian rhythm, as well as altered immunological responses[28]. Some of the long-term effects of these disturbances include not only a reduction in the total hippocampal volume and reduced rates of neurogenesis, but also an accumulation of visceral fat and obesity, a higher susceptibility to insulin resistance, and an increase in the production of inflammatory cytokines, which lead to cardiometabolic diseases[29].

To our knowledge a direct influence of dietary habits on the HPA-axis has not been reported, however some authors suggest that the gut-microbiome could mediate these effects[30]. Clinical and biochemical evidence has concluded that alterations in the diversity and particular strains of bacteria comprising the microbiome, also known as dysbiosis, modulate the negative effects of stress on the HPA axis at different stages of life[31]. A particular study on marital-related stress reported an increased release of lipopolysaccharides (LPS) originating in the gut microbiome, as a result of dysbiosis, with a dose-response relationship[32]. LPSs cause damage to the gut-membrane and lead to major adverse cardiovascular events as demonstrated by Pastori *et al*[33] in 2017. Moreover, damage to the gut membrane results in the translocation of LPSs into the plasma, where they stimulate the differentiation of T-cell lymphocytes, further promoting inflammatory mechanisms[33,34]. Although the objective of the study was to assess the associations between circulating LPS and major adverse cardiovascular events, similar biological mechanisms have been identified in patients with depression [35]. Given the lack of clinical trials in this particular matter, incident depression has been inconsistently associated with cytokines such as LPS and others[35]. Hence, the true nature of this relationship has yet to be explained.

Dietary determinants of dysbiosis include fiber, fatty acid, and probiotic intakes[30, 36,37]. In fact, dietary interventions have demonstrated that changes in the microbiome are possibly due to these food items, however incident depression has not been assessed concomitantly[38,39]. Results in a Korean study evaluating dietary fiber and prevalent depression demonstrated significant inverse associations between cereal, seaweed and mushroom fiber, and depressive symptoms[40]. Despite these encouraging findings, significant associations with prevalent depression were only found for the consumption of seaweed fiber (multivariable-adjusted OR 0.45 (95%CI: 0.23-0.88) for the comparison of quartile 4 *vs* quartile 1 of intake)[40]. Additionally, microbiome changes are highly dependent of the pre-existing diversity of bacteria in the gut. As stated by others, the microbiome demonstrates a resilience to change which

is not yet fully understood[41]. Hence, additional research is needed before general recommendations can be made.

Monoamines

Another widely accepted aetiological theory of depression focuses on the role of monoamine synthesis and activity. Indeed, lower concentrations of these monoamines (serotonin, dopamine and noradrenaline) have long been associated with depressive symptoms and ultimately with depressive disorder. Altered monoamine activity is driven by inadequate production and their rapid degradation in the pre-synaptic space [5]. However, some inconsistencies remain unanswered regarding this hypothesis. Primarily, the prolonged response time observed for typical antidepressants which reduce depressive symptoms weeks after initiating treatment despite a normalization of monoamine levels in just a few hours[42,43].

Monoamine production is primarily dependent of vitamin B-6, folate, and vitamin B-12 Levels as precursors[44]. These micronutrients are essential in the metabolism of S-adenosyl methionine and methionine, both of which are critical for monoamine production and other methylation processes within the brain[44]. Sub-optimal levels of folate and B-group vitamins have been associated with higher homocysteine concentrations, which in turn are associated with depressive disorders, Alzheimer's disease, and altered cognitive disfunction[45]. The role of homocysteine in the hypothesized biological mechanisms of UDD is based on the direct vascular damage and excitotoxicity exerted by its metabolites (homocysteinic acid or cysteine sulfinic acid).

Specific examples of the effects of individual foods on monoamines are scarce, however increased serum levels of dopamine and serotonin have been documented in response to dietary restrictions or supplementation with cocoa extracts[46,47]. Monoamine activity is also dependent on its enzymatic degradation by the monoamine oxidase enzyme (MAO) in the pre-synaptic space; a staple target for antidepressant drug therapy. In particular, the MAO-B variant of this enzyme is susceptible to dietary interventions as demonstrated by Zellner *et al*[45]. This study demonstrated that an increase in vitamin B12 was correlated with a lower MAO-B expression (median expression reduction of 26%, adjusted P value < 0.05). In this three-week dietary intervention, a significant reduction of MAO-B was achieved through a high protein diet (approximately 3.0 g of protein/kg per day) primarily consisting of meat products (55% of total protein intake). Based on these observations, B-group vitamin supplements are theorized to have an antidepressant activity as noted in some *in vitro* and *in vivo* studies[48,49]. B-group vitamins are crucial for the transformation of homocysteine into methionine through the 5-methyltetrahydrofolate pathway[44], however vitamin B12 supplementation has not been uniformly associated with reduced UDD risk nor symptom improvements. Some clinical trials have noted elevated concentrations of homocysteine and low levels of B-group vitamins in depressed patients at baseline[50-52]. However, two interventions with B-vitamin supplements (the shortest consisting of two years, in a sample of n = 2919 geriatric patients with major depressive disorder) observed non-significant improvements in depressive symptoms[51,53]. Positive reports have been found under particular conditions, yet strong and reproducible evidence is warranted for the widespread use of vitamin B12 supplements as an inexpensive aid to pharmacological treatments[47,54]. Furthermore, a comparative analysis on the effect of folates and B-group vitamins should be conducted controlling for homocysteine reduction and increased monoamine activity through MAO-B suppression. Lastly, when considering the effects of dietary interventions on depressive symptoms, the overall antioxidant properties of a healthy dietary intervention should be considered.

Neurotrophism and neuronal activity

Although few reports exist on the effects of neurogenesis in the development of UDD, initial studies highlight the central role of the brain derived neurotrophic factor (BDNF). BDNF is synthetized and secreted primarily by endothelial cells[55] and is necessary for neuronal development as demonstrated in animal models[56]. The initial transcription and translation of the BDNF gene produces an immature molecule (prepro-BDNF) which is then converted into pro-BDNF and eventually transformed into mature BDNF through a series of protease enzymes[57,58]. Although prepro-BDNF has not been attributed biological activity, pro-BDNF can bind to the p75 neurotrophin receptor (p75NTR) and induce cell senescence in the hippocampus and prefrontal cortex[57-59]. Mature BDNF, on the other hand, has been related to the maturation of neurons, establishment of synaptic connections (through axonal growth and neuronal survival), and interestingly neural plasticity[56,57,60]. Such mechanisms, however, are highly dependent on the site of the brain in which they occur[59]. BDNF

secreted into the amygdala and nucleus accumbens has been found to worsen depressive symptoms, whereas the opposite is true in the prefrontal cortex and hippocampus, both in human and animal models[57,58]. The site-specific activity of BDNF was initially thought to be the cause of reduced hippocampal volume, as described in post mortem studies in patients with depression[59,60]. These findings have since been attributed to a single nucleotide polymorphism resulting in the translation of Methionine and not Valine-66 ($Val^{66}Met$), which hinders the transformation of proBDNF to BDNF[59]. However, the lower hippocampal volume hypothesis has been thoroughly criticized in a recent meta-analysis which highlights the low statistical power of the available evidence, plausible publication bias, and tendency towards the null value of current evidence[61]. Post-mortem studies on patients with depression have also found lower BDNF levels, lower expression of the BDNF receptor (*TrkB*), and an increased expression of p75NTR in the hippocampus (particularly in suicide patients), all of which correlate to negative effects on depressive symptoms[60,62]. Finally, BDNF has also been suggested to be a mediator of certain antidepressant therapies, such as electroconvulsive therapy and antidepressant drugs[56,58]. In the particular case of fluoxetine, mice with the knock-in $Val^{66}Met$ variant were completely void from the antidepressant effects of the drug[58]. A major debate in regard to antidepressants has been their delayed effects, leading some researcher to believe that BDNF activity is responsible[58]. This theory is based on the effects of antidepressants on BDNF levels, which stimulate neuronal plasticity and improve neuronal synapse in the hippocampus after a period of time; corresponding with the cessation of depressive symptoms[56].

In relation to diet, post mortem studies report lower levels of retinoic acid receptor-α (RARα) in the prefrontal cortex along with disturbances in the *TrkB* pathway[62]. Qi *et al*[62] found that retinoic acid and vitamin A sub-species, could stimulate the *TrkB* promoter in an *in vitro* study and potentially improve depression management. Similar to BDNF, vitamin B12 has shown to selectively promote the expression of the BDNF-receptor gene (*Ntrk-2*) in the prefrontal cortex[48]. Despite observing no significant increase of these receptors in the hippocampus, an acute vitamin B12 supplementation counteracted the stress induced alterations of *Ntrk-2* expression and depressive behavior in mice[48].

Given the novelty of these findings, few reports exist on the human effects of BDNF, and fewer which attribute its activity to dietary interventions. To our knowledge, only the PREDIMED (*PREvención con DIeta MEDiterranea*) trial has reported on the changes of BDNF as a result of a dietary intervention. In the PREDIMED trial, subjects allocated to the MD pattern and supplementation with nuts were less likely to have lower BDNF levels[63]. Moreover, after three years of intervention, a statistically significant increase in BDNF was observed among participants with prevalent depression and allocated to the MD supplemented with nuts. The results suggest that in patients with prevalent depression, BDNF concentrations are influenced by dietary interventions[63]. Despite the success observed in the dietary intervention of the PREDIMED trial, the complexities, regulatory mechanisms, and site-specific neuronal activity of this neurotrophin demand an in depth understanding of its implication in UDD.

Health related quality of life

One of the main reasons for UDD treatment is to improve patients' health related quality of life (HRQoL), however, this goal has proven difficult to achieve and understand. The perception of health has been broadly studied under two main physical and mental domains since the 70's[64]. In addition to overall health, external factors contribute greatly to this subjective concept. Bidirectional relationships between HRQoL and UDD have been reported, however, cause-effect relationships remain inconsistent. Some reports include reduced HRQoL at baseline for patients with UDD, in whom perceived health improves after anti-depressant treatment[65,66]. It should be mentioned that not all pharmaco-therapies improve well-being, possibly due to secondary effects or treatment related stress[66]. Hence the need for additional research. Moreover, if HRQoL does not improve, persistent perceived health reduction could worsen UDD and even increase suicide risk[5,67]. Various physical, mental and socioeconomic factors have been identified as determinants of increased suicide risk, all of which contribute varying effects[68]. In these matters, psychotherapy, particularly behavioral cognitive therapy, has proven to be an effective measure to improve HRQoL[69,70]. Unfortunately, these improvements have been limited to mental domains, which could indicate that additional factors are not being considered. On the other hand, diet has been cross-sectionally associated with both physical and mental domains of HRQoL[71-73]. Furthermore, nutrient deficiencies have been related to

worsened perceived health, whereas healthy dietary habits seem to improve HRQoL across various age-groups[74,75]. Research in this particular field is scarce, but initial results are beginning to shed light on these associations. A report by Gariballa *et al*[76] in 2013 found that in addition to changes in homocysteine levels, a significant improvement in HRQoL was observed. The added value of improving HRQoL is not only an effective measure of patient health, but also of the quality of medical care. Clinical trials and prospective studies should focus on the potential mediator effect of nutritional status on the association between depression-related clinical outcomes and perceived health (UDD - Diet - HRQoL).

In the following table (Table 1) a summary of the primary aetiological hypothesis and mechanisms involved in depression are summarized. Furthermore, one-to-one associations and evidence of the potential effects of diet on each of these mechanisms is presented.

LINKS TO OTHER CARDIO-METABOLIC DISEASES

Along with UDD, cardiometabolic diseases are amongst the top causes of global burden of disease (GBD)[2]. Based on the mechanisms previously described, more and more evidence supports the role of diet and lifestyle as key determinants of mental health, quality of life, and cardiometabolic disorders[3]. Around the world, unbalanced diets, consumption of sugary beverages, and fast foods have been associated with and increased risk and presence of metabolic disturbances such as elevated fasting plasma glucose, and high blood pressure[77]. Sedentary behavior, a mayor cause of obesity and metabolic syndrome, has been associated with an increased risk for various mental disorders[7]. These observations further reflect the implications of (poor) lifestyle patterns habits on physical and mental health, both of which flourish under similar biological conditions. Likewise, the chronic pro-inflammatory state present in metabolic syndrome is the ideal scenario for glucose intolerance, lower insulin secretion, and the accompanying glucocorticoid dysregulation that precedes the onset of diabetes[78-81]. The cycle of damage persists once these changes have been established due to the detrimental effects of pro-inflammatory cytokines across various organs and systems, including pancreatic β-cells, endothelial cells, various strains of immune cells, among others. Unfortunately, advancements have been limited, however, biomarkers such as the myokine irisin are beginning to emerge as bridging biomarkers both in UDD and cardiometabolic diseases. This myokine, also produced in the adipose tissue, has been found to be a potent predictor of post-stroke depression in addition to solid associations with physical exercise and adiposity[82]. Considering these interactions, it is not outlandish to argue that the actual impact of depression has been underestimated, as prior researchers have suggested[83,84].

WHY A MD PATTERN FOR THE PREVENTION OF DEPRESSION?

The literature surrounding the MD and its characteristics is vast and well documented. When referring to the MD, researchers address a pattern of dietary characteristics and lifestyle found in countries of the Mediterranean basin, specifically in the 1960s[85]. In this geographical and temporal period, diets were characterized for their high consumption of olive oil (as primary source of dietary fats), nuts, fatty fish, local seasonal fruits and vegetables, in addition to a low consumption of meat (with a preference for poultry rather than red meats), dairy products, sugared beverages and confectionary/baked goods, and a moderate consumption of red wine. Furthermore, traditional culinary practices such as the "sofrito" (a tomato and olive oil-based sauce with various vegetables) enhance not only the flavors in this dietary pattern but also their innate nutrients. For the purpose of nutritional epidemiological studies, dietary questionnaires have been developed to assess the consumption of key foods and culinary techniques of this dietary pattern. Pioneering to this field was the development of the MD score (MDS) by A. Trichopoulou and collaborators, which considers the consumption of 9 key foods characteristics of the MD[86,87]. More recently, the 14-item questionnaire developed for the PREDIMED trial is the most wide-spread questionnaire evaluating the adherence to the MD pattern and its health benefits[88]. A novel, more precise approach is presently being developed with the inclusion of metabolomic assessment in order to objectively ascertain adherence to the MD. These analyses are based on the identification of key end-products of human

Table 1 Summary of aetiological hypotheses and nutritional determinants of depression

Aetiological Hypotheses	Main mechanisms	Biological disturbances in UDD	Relationship with Diet	Ref.
Oxidative stress and inflammation	Higher cytokine levels in patients with UDD induce BBB damage and increased permeability to the brain, mainly through claudin 5 dysfunction. Furthermore, oxidative stress and cytokines stimulate the vagal nerve, further promoting a pro-inflammatory in the CNS.	Increased IL-6, TNF-a, C-reactive protein, INT- γ, and other inflammatory cytokines. BBB damage and translocation of cytokines and immune cells into the brain.	Adequate antioxidant intake and lifestyle habits prevent the development of a pro-inflammatory state.	[16,17, 19]
Glucocorticoids and HPA-axis	Chronic stress leads to the constant release of cortisol and eventually a down regulation of cortisol receptors in the hypothalamus. In addition, altered immune responses promote further neuronal damage and other metabolic diseases.	Increased basal cortisol and LPS.	Healthy gut microbiomes prevent the release of LPS and other cytokines into the plasma, limiting the potential damage of stress and theoretically decreasing UDD risk.	
		Altered cortisol circadian rhythm.		
		Secondarily, T-cell differentiation and release of inflammatory cytokines.		
Monoamine activity	Inadequate monoamine production and an increased degradation rate, mediated by the MAO enzyme, are related to depressive symptoms. Although current therapy is based on improving monoamine availability in the synapsis, uncertainties remain regarding this hypothesis.	Reduced monoamine formation and activity.	Vit-B12 and folate are necessary for monoamine production.	[28,29, 33,34]
		Homocysteine (also homocysteinic acid or cysteine sulfinic acid) has detrimental effects on neurons.	Homocysteine accumulation is a result of Vit-B12 deficiency.	
			MAO-B activity has been associated with Vit-B12 levels and dietary practices.	
Neuronal development and activity	Altered BDNF function is caused by oxidative stress and inadequate endothelial function. This neurotrophin is essential for neuronal development, synapse formation and cerebral plasticity, in addition to having anti-depressant effects. However, its antidepressant effects are dependent on brain region and therefore not fully understood	Altered BDNF activity and other markers of endothelial function (IL-6, TNF-a, ICAM-1 and VCAM-1).	Antioxidants, MUFA, and PUFA concentrations regulate endothelial function.	[44–46]
		Decreased post-mortem hippocampal and prefrontal cortex volumes.	Vit-B12 promotes the expression of genes that code for BDNF-receptors (Ntrk-2).	
The role of Health Related Quality of Life	Lower HRQoL has been associated with depression relapse and increased risk of suicide.	HRQoL is generally lower in patients with depression. Furthermore, pharmacotherapy improves mental components of HRQoL.	Quality of diet has been direct and cross-sectionally associated with HRQoL scores. The effects of diet on homocysteine level influence HRQoL and thus, potentially improve UDD patient status.	[55,57, 62,63]

UDD: Unipolar depressive disorder; IL-6: Interleukin 6; TNF-α: Tumoral necrosis factor-α; INT- γ: Interferon- γ; HPA-axis: Hypothalamus-pituitary-adrenal axis; LPS: Lipopolysaccharides; MAO: Monoamine oxidase; BDNF: Brain derived neurotrophic factor; ICAM: Intercellular adhesion molecule; VCAM: Vascular adhesion molecule; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; HRQoL: Health related quality of life.

metabolism that prevail when an individual adheres to this dietary pattern; also referred to as the "metabolic signature" of the Mediterranean diet[89].

The cardio-protective effects of the MD are mainly attributed to its anti-inflammatory and antioxidant properties. For this and other reasons, the American College of Cardiology and the American Heart Association amply recommend this dietary pattern in their 2019 guidelines[90], in addition to its inclusion in the Dietary Guidelines for Americans 2020-2025. All three institutions advocate for dietary patterns which emphasize the consumption of seafood, vegetables, fruits and nuts for the prevention of cardiovascular disease. However, in relation to UDD, the 2015 American dietary guidelines advisory committee deemed the evidence on the risk reduction of depression to be limited in its actual state[91]. When compared with other dietary patterns, the MD provides adequate concentrations of most micronutrients, particularly antioxidant compounds[92-94].

Based on these characteristics and reflecting on the biological hypotheses previously described, we could argue that the MD could also be beneficial for UDD prevention.

Epidemiological studies have found that these compounds exert positive effects on endothelial function and inflammation based on biomarkers such as TGF-β1 and IL-6, ICAM-1 VCAM-1, among others[95]. As evidenced in the study by Sánchez-Villegas *et al*[63] in 2011 a dietary intervention with a MD supplemented with nuts in patients improved BDNF concentrations in patients with prevalent depression. Additional benefits to the endothelium of cardiovascular and neural cells originate from the adequate ratio of "healthy fats" in this dietary pattern [reflected in the mono- and polyunsaturated fat (MUFA/PUFA) and mono- and saturated fat (MUFA/SFA) ratios][96,97]. Among the most researched effects of fatty acids on membrane function surround the effects of Omega-3 fatty acids (also n-3). N-3 fatty acids include are polyunsaturated fatty acids (PUFA) that derive from alpha linolenic acid. The two primary forms of n-3 are eicosapentaenoic (EPA) acid and docosahexaenoic (DHA) acid, both of which are found in seafoods. EPA in particular plays a critical role in the adequate functioning of dendritic and synaptic membranes, hence its advised supplementation for patients with UDD[74,98]. In this line, DHA is an integral component of macular and dendritic cell membranes, further supporting its supplementation[6,99]. Consumption of fish and nuts in the MD has demonstrated to improve overall lipid composition (n-3 and other unsaturated fatty acids instead of trans-fatty acids or saturated fatty acids) which ensures adequate membrane functioning[6,98].

Folate and vitamin B12 intake are a major concern for subjects following plant-based diets. Nonetheless, nutrient deficiencies were scarce in a sample of free-roaming individuals adhering to the MD[93]. These micronutrients are critical for BDNF function but also necessary for an adequate production and activity of monoamines. Green leafy vegetables, legumes, grains, nuts and fruits within the MD have a high nutritional value for their folate and vitamin B12 content as well as other nutrients, such as fiber, vitamins, and minerals. Most of these foods are responsible for the positive effects of the MD on gut microbiome, further evidenced by improvements in insulin sensitivity and diabetes risk[100,101]. In this study, it was estimated that the prevalence of vitamin B12 deficiency among the 4th and 5th quintiles of adherence to the MD was 1%. Hence, the prevention of UDD by a MD pattern has been partially attributed to this dietary pattern's adequate intake of vitamin B12[102]. This was further supported by a comparison between categories of MD adherence and UDD incidence risk; compared to the lowest adherence to the MDS, the top 4 categories were associated with a risk reduction for incident depression of 26%, 34%, 51% and 42%, respectively[8], observing a significant dose-response relationship[8,103]. Although subject to debate, caloric restriction has been demonstrated to play a role in UDD and aide in the progression of non-alcoholic fatty live disease[104]. Hunger-related stress induced anti-oxidant effects in the brain through increased blood flow and the removal of damaged cellular organelles. Interestingly, the hippocampus is particularly benefited from the increased perfusion, resulting in an increase in neurogenesis mediated by BDNF and a decrease in apoptosis rates[105,106]. However, this theory would imply that the release of glucocorticoids and the subsequent HPA-axis activation, as a result of stress, is also capable of promoting neurogenesis despite its impairment in patients with depression. In a meta-analysis, the mean weighted effects of a very low calorie diet on depressive symptom scores revealed a Hedges' g = −0.728 (95%CI: −1.204, −0.253)[107]. These results were further analyzed in order to understand the mediator effects of exercise, duration of the caloric restriction, and cognitive behavioral therapy. It was concluded that exercise and longer duration of caloric restrictions partially explain the improvements in depressive symptoms, but more importantly, the exclusion of behavioral therapy yields no significant improvement of symptoms[107]. These mechanisms and the UDD hypotheses to which they are linked, have been summarized in Figure 1.

These promising reports signal an under-developed field for UDD prevention, however, the long-term psychiatric effects that could arise from the severe acute respiratory syndrome coronavirus 2 pandemic demand for an exponential development of this knowledge. Front line workers should be considered at a double risk for COVID-19 and psychiatric disorders as suggested by the high prevalence of anxiety and burn-out in this group, with serious implications for the health and well-being of the population in general[108,109].

Some of the most noteworthy results from observational studies and clinical trials regarding the role of the MD, individual nutrients, and foods on incident depression are summarized on Table 2. This summary includes studies conducted in the *Seguimiento Universidad de Navarra* (The SUN study), studying the associations between diet and lifestyle with incident depression.

Table 2 Summary of the effects of various nutrients, food groups, dietary patterns and lifestyle on prevalent or incident depression

Dietary components	Total/number of cases	mean follow-up *t* (yr)	Main Results[1] [comparisons between quantiles (q) or the designated categories]
Cohort studies			
Nutrients			
Omega-3 fatty acids[6]	7903/512	2.4	q4 *vs* q1: OR (95%CI) 0.65 (0.47–0.90). *P* for trend = 0.376
Trans fatty acids[37]	12059/657	6.1	q5 *vs* q1: 1.42 (1.09-1.84); *P* for trend = 0.003
MUFA[37]	12059/657	6.1	q5 *vs* q1: 0.80 (0.62-1.03); *P* for trend = 0.05
PUFA[37]	12059/657	6.1	q5 *vs* q1; 0.76 (0.59-0.99; *P* for trend = 0.03
Magnesium[123]	12939/737	6.3	q5 *vs* q1: 1.11 (0.77-1.59) No association.
Nutritional adequacy[124]	13983/953	8.5	≥ 4 nutritional deficiencies *vs* ≤ 1: 1.37 (1.01-1.85)
Total Fiber[40]	548/198	Cross-sectional	q4 *vs* q1: OR = 0.54 (95%CI: 0.11–2.63); Non significant association
Foods and food groups			
Fast food[125]	8964/493	6.2	q5 *vs* q1: 1.36 (1.02-1.81); *P* for trend = 0.03
Ultra-processed foods[126]	14907/774	10.3	q4 *vs* q1: 1.33 (1.07, 1.64); *P* for trend = 0.004
Baked goods[125]	8964/493	6.2	q2-5 *vs* q1: 1.38 (1.06-1.80);
Olive oil[37]	12059/657	6.1	q5 *vs* q1: 0.80 (0.62-1.04); *P* for trend = 0.06
Seafoods[127]	6587/1367	Cross-sectional	q3 *vs* q1 of fatty fish consumption: OR 0.72 (0.59–0.88). Higher intakes were non-significant
Coffee[128]	14413/199	10	≥ 4 cups/d *vs* < 1 cup/d: 0.37 (0.15–0.95); *P* for trend = 0.220
Yoghurt[36]	14542/727	9.3	Low fat: max *vs* min: 1.32 (1.06–1.65); *P* for trend = 0.001
			Whole fat: max *vs* min: 0.78 (0.63–0.98); *P* for trend = 0.02
Dietary patterns			
MD score[8]	10094/480	4.4	3pts *vs* 0-2pts: 0.74 (0.57-0.98)
			4pts *vs* 0-2pts: 0.66 (0.50-0.86)
			5pts *vs* 0-2pts: 0.49 (0.36-0.67)
			6-9pts *vs* 0-2pts: 0.58 (0.44-0.77); *P* for trend <0.001
MD score (updated)[103]	15093/1051	8.5	q5 *vs* q1: 0.84 (0.69-1.02); *P* for trend = 0.001
Pro-vegetarian[103]	15093/1051	8.5	q5 *vs* q1: 0.74 (0.61-0.89); *P* for trend < 0.001
AHEI 2010[103]	15093/1051	8.5	q5 *vs* q1: 0.60 (0.49-0.72); *P* for trend < 0.001
DASH-Fung diet[102]	14051/410	8	< 2pts *vs* 3-9pts: 0.76 (0.61-0.94):
Pro-inflammatory pattern [129]	15093/1051	8.5	q5 *vs* q1: 1.47 (1.17, 1.85); *P* for trend = 0.010
Lifestyle			
Mediterranean lifestyle [130]	11800/806	8.5	High *vs* low : 0.50 (0.32-0.81)
Healthy lifestyle score[131]	14908/774	10.4	Max *vs* min: 0.68 (0.49-0.95); P for trend 0.010
Alcohol[132]	13619/459	8	Moderate *vs* no consumption: 0.62 (0.43-0.89) in female subjects
CV risk equation[133]	16739/927	6	q5 *vs* q1: 3.45 (2.40-4.95) starting at 40 yr
Physical activity[7]	10381/923	6	q5 *vs* q1: OR (95% CI) 0.81 (0.65-1.00) *P* for trend < 0.01
Leisure time physical activity[134]	6343/311	10.5	> 20 METs-h/wk *vs* < 10 METs-h/wk; 0.84 (0.72–0.99); *P* for trend 0.046
Tobacco[135]	8556/190	4	Smokers *vs* non-smokers: 1.30 (0.97-1.73)
Childhood obesity (5 yr) [136]	11825/651	6.1	Obese *vs* low weight: 1.50 (1.06-2.12); *P* for trend = 0.012

Youth obesity (20 yr)[136]	11825/651	6.1	Obese *vs* low weight: 2.22 (1.20-4.08); *P* for trend = 0.005
Clinical trials			
The PREDIMED study [119]	3923/224	5.4	MD + EVOO[2] or nut supplements *vs* Low fat diet: multivariable adjusted 0.85 (0.64 to 1.13); Non significant associations
The MoodFOOD Study [117]	512/54	1	Multi-nutrient supplement *vs* placebo groups: OR = 1.06 (0.87-1.29); Non significant associations.

[1]Estimates are presented as HR (95%CI) for incident depression unless stated otherwise.
[2]Extra virgin olive oil. MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; MD: Mediterranean diet.

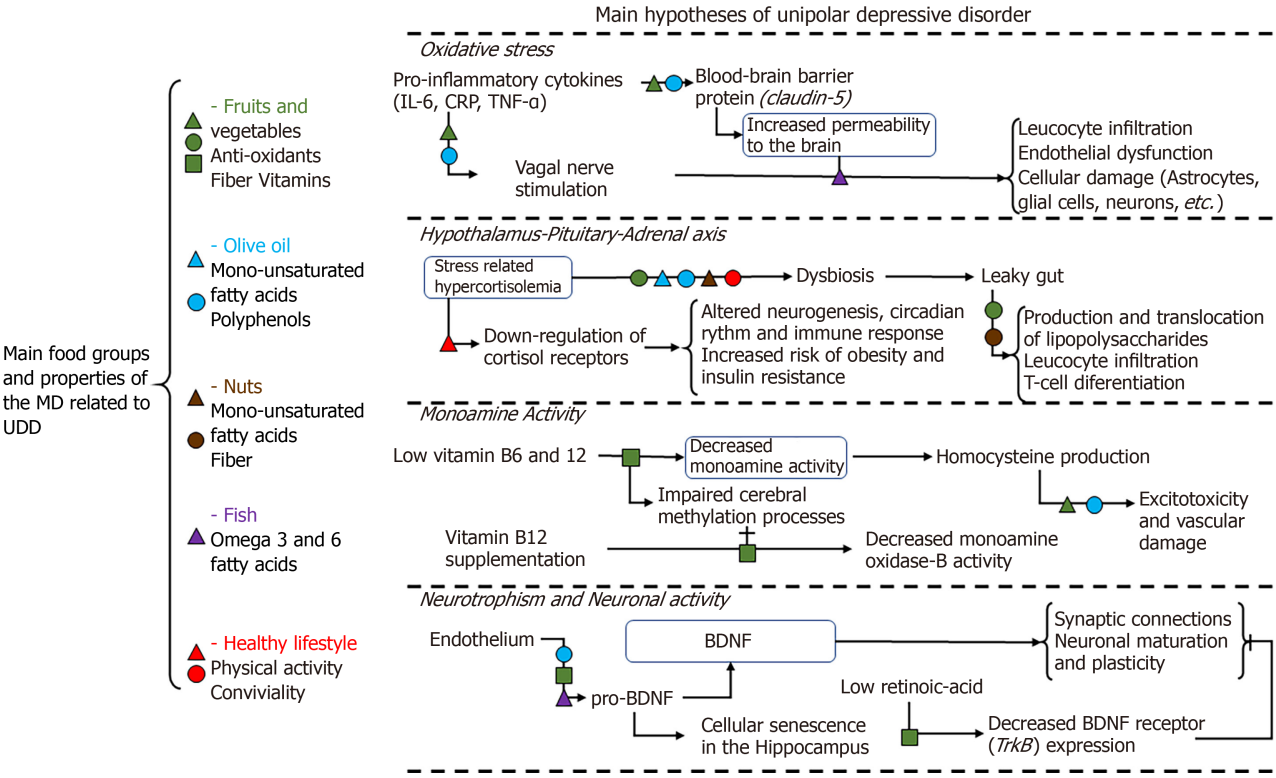


Figure 1 Summary of interactions between the Mediterranean diet and the unipolar depressive disorder hypotheses. On the left side of the panel are the main food groups and their bioactive compounds, with known interactions with unipolar depressive disorder pathways. Each bioactive compound has a designated figure and color. The right side of the panel summarizes the aetiological hypotheses of depression and the main contributors to the disease. Black arrows designate the sequence of biological events in each mechanism, whereas "T" shaped lines designate an inhibitor effect. The figures designated for each compound are located within the sequence of biological events to designate the site of interaction with these mechanisms. See the main text for a detailed description of these interactions and associations. MD: Mediterranean diet; UDD: Unipolar depressive disorder; IL-6: Interleukin-6; CRP: C-reactive protein; TNF-α: Tumor necrosis factor-α; BDNF: Brain-derived neurotrophic factor.

Epidemiological evidence supporting MD

In recent years epidemiological evidence on the benefits of the MD on UDD include several studies both within and outside the Mediterranean area. In the InChianti cohort study including 1362 participants aged 18-102 years, adherence to a dietary pattern rich in vegetables, olive oil, grains, fruit, fish and moderate in wine and red and processed meat, labelled as the 'typical Tuscan dietary pattern', was associated with a reduction in depressive symptoms over a 9-year follow-up period[99]. In the Greek center of the EPIC cohort, a total of 732 men and women 60 years or older were analyzed to determine the association between risk factors for cognitive function and depressive symptoms in the elderly. Adherence to the Mediterranean Diet, as well as olive oil consumption were associated with better scores in both outcomes[110]. Some non-Mediterranean reports include the study by Rienks *et al*[111]. In this study, the authors found that a Mediterranean-style diet was inversely associated with both prevalence (cross-sectional analysis) and incidence of depressive symptoms (longitudinal analysis) with an overall risk reduction of 17% among a sample of mid-aged women from the Australian Longitudinal Study on Women's Health. In the Chicago

Health and Aging Project, MD adherence was associated with a reduced number of new depressive symptoms over 7.2 years of follow-up; 98.6% fewer symptoms among subjects in the highest tertile of adherence compared with those in the lowest[112].

So far, most of the evidence on diet and UDD derives from cross-sectional studies which could lead to false inferences of causal relationships. Furthermore, methodological analyses must address potential confounding, such as the adherence to a particular dietary pattern as a result of a recent diagnosis of chronic diseases or the co-occurrence of lifestyle-related and sociodemographic factors. These issues could be solved by carrying out large randomized trials with interventions based on changes in the overall food pattern. As of today, only small intervention trials have been carried out attempting to prove these and other hypotheses. The SMILES study was an intervention trial that promoted a healthy diet based on Australian and Greek dietary guidelines. In this trial, a dietary intervention with MD significantly improved depressive symptoms as an aid for standard acute depression treatment[113,114]. Focused on an elderly sample, the MedLey study aimed to determine the effect of an intervention with a Mediterranean dietary pattern on this population's cognitive function, depressive symptoms, and quality of life. Despite significant improvements in endothelial function and MD adherence, the study showed no improvements in depressive symptoms nor quality of life after six months of intervention[115]. Examples of multi-country intervention trials include the MooDFOOD prevention trial which examined the feasibility and effectiveness of two different nutritional strategies (multi-nutrient supplementation and food-related behavioral change therapy) to prevent depression. The trial included individuals who were overweight, highly burdened with depressive symptoms, but did not meet clinical criteria for an episode of major depressive disorder in the last 6 mo[116]. In comparison to the placebo, micronutrient supplementation and behavioral therapy failed to prevent incident depression[117].In contrast to these results, the HELFIMED trial has shown promising results in patients with self-reported depression. In this trial, a MD intervention supplemented with fish oil for 6 mo significantly improved depressive symptoms and quality of life[118]. To this day, the PREDIMED study is the longest trial (mean follow-up of 5.4 years) evaluating the effects of a dietary intervention on the risk of incident cases of clinical depression. In this trial the relative risk (RR) estimates for an intervention with MD supplemented with extra-virgin olive oil (9% risk reduction) or a Mediterranean Diet supplemented with mixed tree nuts (22% risk reduction) suggested an inverse association. However, the confidence intervals for both estimates were wide and they showed that the results were compatible with a null result. Even when both Mediterranean diets were merged together and analyzed as a single group, the results were not statistically significant. Only when the analysis was limited to participants with type 2 diabetes (approximately 50% of the sample), a significantly reduced risk of depression was observed only for participants in the group with nut supplementation (significant risk reduction: 41%)[119].

Future research of great interest to this field includes the upcoming results from the PREDI-DEP trial, which was designed to study the impact of the MD on UDD. In this trial, patients over 18 years with a record of a major depressive episode, but with total or partial remission in the previous 6 mo, were recruited in four centers across Spain. With a target sample size of 250 participants per arm, subjects were randomly allocated to a MD intervention with supplemental olive oil, or to a control group who received no dietary advice nor supplements. Over the course of 24 mo participants were assessed every 3 mo to evaluate MD adherence (in the group of intervention) and every 4 mo to ascertain changes in depressive symptoms (in the overall sample)[120]. Food frequency questionnaires, HRQoL questionnaires (Short-Form 36), and physical activity questionnaires were administered in addition to blood sample collections, which were collected at baseline, and yearly during two years[121]. The upcoming results of this trial will aide in the endeavor to elucidate the mechanisms behind diet and UDD, in addition to discerning the particular effects of a MD diet supplemented with olive oil on the incidence and overall prognosis of patients at risk for this disease.

INITIAL DIETARY RECOMMENDATIONS FOR THE PREVENTION OF DEPRESSION

Although there are a number of important gaps in the scientific literature to date, existing evidence suggests that a combination of healthful dietary practices (including the adherence to the Mediterranean Diet) may reduce the risk of developing depression. In 2015, a group of experts with several backgrounds (epidemiology,

psychiatry and nutrition) constructed the first Dietary Recommendations for the Prevention of Depression[122]. These dietary recommendations also provide additional and/or concurrent benefits for obesity, cardiovascular disease, diabetes and metabolic syndrome, and essentially pose no risk of harm. (1) "Follow 'traditional' Mediterranean Diet."; (2) "Increase your consumption of fruits, vegetables, legumes, whole grain cereals, nuts and seeds."; (3) "Include a high consumption of foods rich in omega-3 polyunsaturated fatty acids (PUFAs)."; (4) "Limit your intake of processed-foods, 'fast' foods, commercial bakery goods and sweets."; and (5) "Replace unhealthy foods with wholesome nutritious foods."[123]. Recommendations such as these are crucial steps towards a widespread implementation of diets as preventive measures for diseases, such as UDD, with substantial evidence of its benefits on cardiovascular and metabolic diseases.

CONCLUSION

UDD is and will remain a global health issue that researchers should strive to further understand and prevent. To this day, the hypothesized biological mechanisms that drive this disease include oxidative stress, HPA-axis dysregulation, monoamine and overall neuronal function deregulation. Based on analogous mechanisms, the MD could be a safe and inexpensive contributor to primary prevention strategies for depression, as it is characterized by various advantageous cardiovascular health qualities. Some of these properties include adequate B-group vitamin and folate content, promotion of a healthy gut microbiome, and high levels of various antioxidant compounds. Initial observational studies and trials, such as the PREDIMED study, suggest that implementing nutritional measures has an influence on disease risk and symptoms control. However, dedicated clinical trials are required to confirm the initial observations in order to fully support and understand the impact of diet on unipolar depressive disorder.

ACKNOWLEDGEMENTS

The group would like to acknowledge Ms. Maria Soledad Hershey, PhD candidate at the Department of Preventive Medicine and Public Health at the University of Navarre for providing the English language editing certificate and proofreading this manuscript.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 1017-1026

DOI: 10.5498/wjp.v11.i11.1017

ISSN 2220-3206 (online)

MINIREVIEWS

Neurodevelopmental disorders: An innovative perspective *via* the response to intervention model

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Author contributions: Areces D contributed conceptualization; Rodríguez C and Areces D contributed methodology, software; Areces D contributed formal analysis; Rodríguez C contributed investigation; Rodríguez C and Cueli M contributed resources; Areces D and García T contributed data curation; Areces D contributed original draft preparation; Rodríguez C and Gonzalez-Castro P contributed review and editing; Areces D contributed visualization; Rodríguez C contributed supervision, and project administration; all authors have read and agreed to the published version of the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Supported by Ministry of Sciences and Innovation I+D+i Project, No.

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Abstract

Neurodevelopmental disorders are a group of conditions classified together by the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders which include intellectual disability, communication disorders, autism spectrum disorder, attention-deficit/hyperactivity disorder, specific learning disorder (SLD), and motor disorders. SLD is present in many students, who exhibit significant difficulties in the acquisition of reading, written expression, and mathematics, mostly due to problems with executive functions (EF). The present study is a review of the current situation of neurodevelopmental disorders and SLD focusing on the benefits of the response to intervention model (RtI), which allows the combination of evaluation and intervention processes. It also addresses the key role of EF. The importance of adapting RtI to new possibilities such as the use of virtual reality is discussed and a theoretical framework for carrying that out is provided.

Key Words: Neurodevelopmental disorders; Specific learning disorder; Response to intervention model; Virtual reality

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Core Tip: The present study aims to look deeply into detection of and intervention for students with neurodevelopmental disorders. It includes a description of the current situation of neurodevelopmental disorders focusing on specific learning disorder and executive functions as key aspects in students with problems in reading, writing, and mathematics. The study also presents the evaluation and intervention of neurodevelopmental disorders using an approach *via* the Response to Intervention model and provides a novel avenue for implementation related to the use of virtual reality.

PID2019-107201GB-100; and Principality of Asturias, No. FC-GRUPIN-IDI/2018/000199.

Country/Territory of origin: Spain

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: June 5, 2021
Revised: June 18, 2021
Accepted: September 26, 2021
Article in press: September 26, 2021
Published online: November 19, 2021

P-Reviewer: OConnor JC
S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

Citation: Rodríguez C, Areces D, García T, Cueli M, Gonzalez-Castro P. Neurodevelopmental disorders: An innovative perspective *via* the response to intervention model. *World J Psychiatr* 2021; 11(11): 1017-1026
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1017.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1017

INTRODUCTION

In recent years, one of the most pressing concerns at both national and international level has been achieving more effective education of students with neurodevelopmental disorders. This is evident in educational legislation and current social policies and has led education professionals to develop multiple activities in order to enhance student performance. This has meant dealing with diversity along with growing interest in the field of neurodevelopmental disorders and the students who suffer from them in one way or another[1]. Aware of this reality, the research field has produced a huge number of initiatives to help easily identify students who may be at risk of suffering from problems with their learning or their future behaviour at the earliest possible ages. At the same time, these initiatives have attempted to provide teachers with guidance and strategies so that they can provide timely instruction in pursuit of improved student academic progress and satisfactory school adjustment[2].

In this context, the present study aims to make a detailed examination of the detection of and intervention for students with neurodevelopmental disorders *via* a response to intervention model (RtI) framework. First, we describe the situation of neurodevelopmental disorders, focusing on specific learning disorders (SLD). Subsequently, we introduce the RtI model and provide an innovative approach for implementing it.

NEURODEVELOPMENTAL DISORDERS

Neurodevelopmental disorders are a group of conditions classified together by the latest edition of the Diagnostic and Statistical Manual of Mental Disorders[3] due to their common onset during childhood, high comorbidity rate of 20%-80%, and essential overlap of contributing factors across specific diagnoses[4]. This category includes intellectual disability, communication disorders, autism spectrum disorder, attention-deficit/hyperactivity disorder, SLD, and motor disorders.

SLD is a general concern in modern societies, where reading, writing, and mathematics are necessary skills for daily life[5]. However, students with SLD exhibit significant difficulties in the acquisition and use of these key skills (reading, written expression, and mathematics) despite having intact senses, normal intelligence, proper motivation, and adequate sociocultural opportunities.

Children and adolescents with SLD make up the largest group of students with educational needs in most countries[6]. According to the American Psychiatry Association[3] the prevalence of SLD in children across different languages and cultures is 5%-15% with rates of between 4 and 9% for reading deficits, and between 3 and 7% for deficits in mathematics. Bearing in mind the percentages of children exhibiting SLD, it represents one of the biggest focuses of interest in the educational community.

In recent years, research has begun to examine the common relationships and deficits in SLD (reading, writing, and mathematics) in order to better understand how they overlap rather than focusing on a single deficit, and also because findings suggest that children with a deficit in learning frequently exhibit deficits in other domains[7]. In addition, some genetic studies such as Kovas *et al*[8] have produced evidence that difficulties in reading, writing, and mathematics share genetic variations. More specifically, Kovas *et al*[8] found a genetic correlation of .67 between mathematics and reading difficulties which suggests a strong genetic overlap between them. In a meta-analytical review, Daucourt *et al*[9] indicated higher magnitude phenotypic and etiological overlaps between reading and mathematics difficulties. The consideration of common genetic risk factors linking SLD falls under the generalist genes hypothesis, which posits that the same genes underlie all cognitive abilities and disabilities both within and between academic domains[10].

Along these lines, the aetiology of SLD has been studied from general and specific domains. For example, at the specific level, low reading and writing skills have been shown to be related to problems in representation of sounds or phonological understanding, or decoding, whereas low numerical skills have been associated with a deficit in processing quantities or in the mapping of numerical symbols with mental representations of magnitude[11,12]. However, at the general level, researchers have looked at the role of attention, speed of processing, working memory, and executive functions (EF) in general.

The term EF refers to a mix of cognitive and behavioural processes such as planning, problem solving, sequencing, attention, inhibition, cognitive flexibility, and working memory, among others[13]. All of these processes allow good behavioural and emotional regulation, and have been shown to play an important role in learning in different areas such as reading, writing, and mathematics from very early ages.

While there are many different models which have attempted to give an account of the organization or structure of EF, one of the most influential models nowadays is from Miyake *et al*[14]. This model groups the different EF into 3 fundamental components: inhibitory control (also known as impulse control), cognitive flexibility (a range of attentional focus or "set shifting"), and working memory (or the ability to maintain information in mind while using it). According to this model, the different executive components would develop linked to the maturity of the individual. Miyake *et al*[14] indicated that although it is difficult to differentiate between EF at early ages, they seem to emerge separately in preschool ages (from 3-4 years old), and follow different development paths. At these ages, the children are gaining growing levels of voluntary control over attention, while at the same time being capable of keeping and representing certain information in mind, inhibiting certain responses using mental rules, and of responding and changing their focus of attention flexibly[15,16].

This developmental aspect has led to the study of EF as abilities related to school learning, generally in areas of reading, writing and mathematics[17]. Other longitudinal studies have shown the predictive value of EF measured in infancy on academic success in later educational stages[18-21]. The study by Morgan *et al*[19] with a sample of 18080 pre-school children showed how deficits in working memory and cognitive flexibility in pre-school ages posed a risk for the appearance of reading problems and difficulties with mathematics in the first year of elementary education. Similarly Clark *et al*[18] examined a group of 3-4 years old children and found a significant relationship between working memory and inhibitory control at these ages and performance in mathematics at 5 years old. As for reading, Birgisdóttir *et al*[22] found a relationship between various EF measures taken in preschool and reading understanding in first grade. These studies agree on the importance of EF as essential variables in learning, as well as the need to provide validated evaluation measures and intervention programs allowing work with students from early ages. In this context, the RtI model is one of the approaches which has begun to successfully spread in schools, specifically in early years schooling[23,24].

RTI: A POWERFUL NEW MODEL

The RtI model combines educational evaluation and intervention processes for all students within a classroom action system with 3 levels: *Level 1*- all students receive high quality, evidence-based instruction from teachers starting from an initial evaluation; *level 2*- those students who do not respond adequately in level 1 are given more explicit instruction with more frequent follow up; and *level 3*- which is a supplement to levels 1 and 2 applied to those students who need more intensive and explicit teaching to meet their learning needs[25]. Throughout the three levels, students are evaluated in order to determine their progress and needs. Because of this, RtI is recognised as an extremely valuable model, allowing evaluation and intervention to be carried out with reference to a normative group, and given the starting point, evaluating improvement against the students' own performance[26]. Figure 1 shows an example for a design following the RtI model considering the evaluation and intervention points and levels.

Considering the potential of the RtI model, it also represents a substantive change in the conceptualisation of SLD (a broader vision of how it progresses) in lockstep with social change and changes in the guidance this emerging practice refers to. The RtI model acts as both a preventive and palliative model[27], unlike the traditional (ability-achievement discrepancy) model in which it often takes years before children with SLD are treated[28]. The RtI model offers a solution to the main problem of

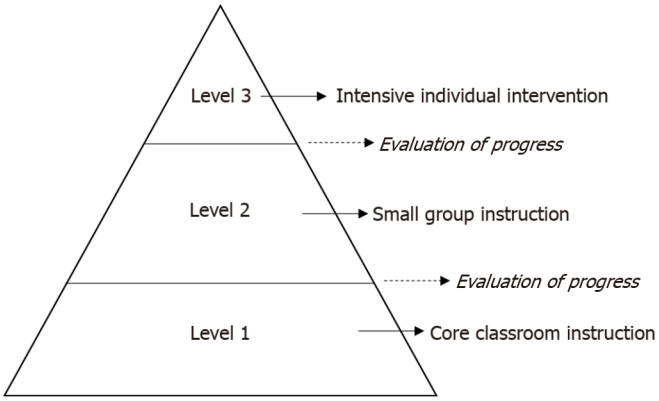


Figure 1 Example of a design based on the response to intervention model considering evaluation points and intervention levels.

previous approaches, as children are detected early and receive appropriate intervention, leading to better prognoses than those whose problems are detected later [1,29]. For instance, in Spain, like in many other countries, an approach based on the ability-achievement discrepancy model is still used to detect students with SLD. These students are usually evaluated and diagnosed from the second year of primary school onwards, when they are already exhibiting significant delays in learning and it is often too late[30]. RtI has the potential to solve numerous problems compared to the ability-achievement discrepancy model (*e.g.*, it provides poorly performing students with individualized instruction, it allows differentiation of students who have true disabilities from students who perform poorly due to lack of proper education)[31].

There is strong empirical evidence of the benefits of using the RtI model in classes in improvement in learning results for all students. Some of those studies focused on achievement in basic academic skills such as writing[32,33], reading[34-36], and mathematics[37]. For example, de León *et al*[38] observed the benefits of implementing the RtI model for intervention with students at risk of failing math. In addition, Jimé nez *et al*[39] analysed the efficacy of an intervention for reading and math within the context of the RtI model. Their results showed that at-risk children in the intervention condition appeared to benefit more than at-risk children in the control condition (who did not receive intervention following the RtI model).

Other studies have focused on promoting RtI to help highly capable students to work to the best of their potential in the classroom[40], as well as students with emotional, social and behavioural needs[41]. In all of those cases, RtI was highly successful as it overlays an approach which includes combined educational evaluation and intervention. The evaluation process covers both initial and final student evaluation, along with all the intermediate progress measures in the skills being worked on. In this way, evaluation and intervention form part of the same continuum in the classrooms. It is only in those cases where the student does not improve, after participating in high quality interventions, that a student proceeds to a more exhaustive evaluation and diagnosis by specialists[42].

In early ages the model allows differentiation between students whose performance is below expectations because of a problem in instruction and those students who really have a neurodevelopmental disorder such as SLD, thus reducing the number of false positives. RtI is considered to be an effective means of determining whether students have received adequate instruction and thereby if their academic skills have improved without needing to be seen by special education services. Furthermore, RtI helps to differentiate as early as possible those students who have not improved despite specific instruction who might not be identified by other models that are less sensitive to intervention, in other words, false negatives[27].

In short, RtI is a promising model allowing the evaluation and identification of individuals with neurodevelopmental disorders such as SLD[43] and intervention according to their levels of need in an inclusive manner.

Considering the benefits of the model, the next question is how to implement the RtI model in relation to EF.

EF AND RTI MODEL

While the RtI paradigm is fundamentally based on the most common causes of difficulties, such as poor phonological awareness or basic mathematical skills, the literature about SLD indicates a wide variety of components that contribute to its appearance and progression, from genetic to cognitive and environmental factors. The literature also shows that focusing on a single component can be a significant restriction to the effective identification and treatment of neurodevelopmental disorders[44]. For this reason many authors have advocated a combined approach which includes evaluation and intervention addressing the cognitive processing areas or EF that may underlie the learning processes in the different areas of reading, writing, and mathematics[45]. Howard *et al*[45] argued that there is sufficient research on the relationship between EF and academic skills and that the evaluation of EF would provide information that would be useful for the design of individualised instruction which is the trademark of special education.

From this combined perspective, Hale an d Fiorello[46] proposed what they called the Cognitive Hypothesis Testing Model, which is based on 4 main premises: (1) Academic performance depends on a large number of complex neuropsychological and cognitive processes; (2) Children normally have unique cognitive and learning profiles, based on different strengths and weaknesses; (3) These learning profiles should be evaluated *via* direct evaluation of the associated cognitive processes as well as *via* the analysis of the response to ecologically valid treatments; and (4) Academic difficulties should be remediated or counterbalanced according to the underlying cognitive strengths and weaknesses. The authors recommended that SLD should be approached from a broad evaluation-intervention perspective, based on problem-solving, and forming part of a continual process which includes RtI and a comprehensive evaluation of cognitive processes.

Despite advances at the theoretical level in this combined perspective of RtI-cognitive (executive) processes, it has not been a well-tried approach at the empirical level to date. The few studies carried out using this approach have so far given mixed results[47]. Furthermore, the design and implementation of new evaluation and treatment models for neurodevelopmental disorders must consider advances in the development of instruments, such as using virtual reality (VR).

VR, A NEW ENVIRONMENT

Using VR improves on the evaluation and intervention systems for disorders such as SLD, offering better ecological validity which leads directly to better specificity and sensitivity than current evaluation tests (thus reducing false positives). VR gives students the perception of being in a virtual environment that is similar to their everyday surroundings, and therefore the (visual, auditory and haptic) sensations and feelings produced will be similar to those in the real classroom[48]. Ultimately, VR is an innovative alternative for performing neuropsychological evaluations of various cognitive processes involved in learning[49,50]. More specifically, in terms of the usefulness of tests in VR, previous research indicates high validity in the evaluation of memory[51], attention[52-55], and other components such as planning and impulse control[56-59]. Numerous studies have demonstrated the advantages of VR for a variety of clinical conditions and groups of healthy participants[58,60-62].

Another great advantage of including VR in current evaluation and intervention systems is that it would allow the student to progress *via* a set virtual experience that adapts to the student's own pace[63]. Various authors have stated that applications using VR have produced higher levels of motivation for learning[64,65]. These findings have even been reported in infant populations (aged between 3 and 4 years old), with not only increased motivation being observed, but also the use of this technology producing better concentration on the relevant stimuli[66].

VR has also been shown to be effective as an intervention tool. Various studies have indicated the advantages of using VR in intervention and rehabilitation programs in infant populations with intellectual disability and cerebral palsy as well as in treating learning difficulties and attentional problems[67-70]. One of the advantages indicated by the users themselves is that VR allows them to train different skills and abilities in a similar way to in the classroom without worrying about what others think of their mistakes and without embarrassment[68].

In short, VR offers the possibility of objectively analysing cognitive variables that are difficult to observe directly in the school environment, and at the same time it

allows tasks to be performed (both evaluation and intervention) with better ecological validity. Researchers often state that VR is more effective than evaluating children in laboratory settings where they are assessed individually, without classmates, under the supervision of an evaluator they do not know[70,71].

To adapt evaluation and intervention tasks to VR environments, one possibility is the innovative hardware from PICO interactive headsets which includes tools that allow the users to move, walk, crouch and do all manner of movements, without degrading the interaction with the virtual environment as there is no physical connection with any other device. With this hardware, a 3D context is created in which the participant is immersed in a natural, dynamic computer-generated environment which allows the creation of similar situations to those that happen in everyday life. In these environments, the type, amount and complexity of the presented stimuli are easily controlled, allowing the design of useful settings to gather objective indicators related to the participants' execution. To achieve this objective, the designers use various technologies such as head mounted displays, tracking systems, headphones, movement sensors, and joysticks. The possibility of controlling all of these stimuli through a multi-sensorial experience, similar to real-life surroundings, increases ecological validity while at the same time maintaining methodological standards *via* the standardisation of the tests[50]. It also has an effect on participants' motivation by giving them a more active, and interactive, role in the evaluation setting[59].

In summary, the features of this kind of hardware together with the advantages of the classic, current evaluation test, would achieve greater reliability and validity in the detection and intervention of neurodevelopmental disorders. Examples of this include the adaptation of classic tests, such as VR-Stroom[72], V-ToL (Virtual Tower of London) and V-Wcst (Virtual Wisconsin Card Sorting Test)[73], along with the creation of new contexts such as the Virtual-Store (V-Store)[73], the Virtual Action Plan-Supermarket (VAP-S)[74], the Virtual Supermarket (VMall)[57], and the well-known Virtual Classroom from Rizzo *et al*[55] and Armstrong *et al*[56].

Along with the complexity of evaluating within the RtI model, the evaluation of EF in the preschool stage is still difficult, especially considering the scarcity of EF assessment tools based on VR for this stage. One possibility for EF assessment in early years may be the adaptation of traditional measures. Examples include the Sorting Task and Animal Shifting (flexibility); the Animal Stroop, The Day and Night task, the Simon Task, and Local Global (inhibition); and Keep Track and Odd One Out (working memory)[16]. At the same time, in order to achieve more effective evaluation and intervention for SLD, VR tests must be adaptive in line with hypermedia systems.

THE NEXT STEP

The origins of educational hypermedia systems are linked to the appearance of the first intelligent tutors[75]. These tutors were student oriented and were based on the combination of study materials and the results of questionnaires, establishing an adaptive sequence for the course. As technology evolved, systems began to be developed known as Adaptive Educational Hypermedia Systems. The main objective of these systems is to adapt themselves to students based on certain characteristics such as what the student knows about the topic and the students' learning styles or learning difficulties[76]. One of the things adaptive hypermedia systems bring to e-learning is the application of an adaptation model called the user model, which is the lens through which the e-learning system organises the visualisation of content, the order of presentation, the level of difficulty, and the type of feedback, based on various parameters (number of correct answers, errors, score, *etc*.)[77]. However the potential of the model applied to neurodevelopmental disorders is still to be developed, from some promising initial results[78,79]. For example, Cueli *et al*[80] observed that students who worked with a hypermedia system in mathematics achieved better results in their knowledge of self-regulatory strategies. In addition, Taub and Azevedo [81] found that the use of hypermedia systems was more beneficial in the case of students with low prior knowledge.

Considering the potential of the RtI model for evaluation and intervention in EF and the benefits of VR and adaptive hypermedia systems, the future of evaluation and intervention in neurodevelopmental disorders should combine all of these main aspects. The challenge is to combine all of these new approaches (RtI, VR, and adaptive educational hypermedia systems) in order to improve EF in SLD students and incorporate this combination in schools. This will mean a new role for teachers who will have to support the process and the students at the evaluation points and in

the intervention levels that are currently part of RtI but with the new possibilities provided by VR and adaptive educational hypermedia systems.

CONCLUSION

The potential benefit of the RtI model is that, through its dynamic evaluation-intervention-evaluation processes, it is an effective system for measuring the progress and achievement of students who are lagging behind. It is also a safe method for monitoring low achievement in all students, whether due to lack of interest or motivation, boredom, or any other factor influencing insufficient learning[40]. The continued use of RtI in the classroom also aims to help children of average ability who present emotional and behavioural problems[41]. When a child is found to be exhibiting maladaptive behaviour or negative behaviours they are also evaluated and, depending on the results, evidence-based educational practices are added to reduce these behaviours and to promote positive attitudes towards the child's social and academic life.

The scientific evidence indicates that students' social and emotional competencies also play a key role in producing appropriate development and successful learning[78,79,81]. Nevertheless, when children begin to exhibit difficulties in language and other academic areas, they run a high risk of their socio-emotional abilities deteriorating [24]. For example, children with SLD who are not dealt with early often begin to develop less involvement in school activities, by not paying sufficient attention to instructions and by interacting less with their classmates, which can lead to delays in learning and achievement and increased likelihood of developing behavioural problems. Because of that, RtI has become a model of pedagogical action that is able to meet these students' needs so that they can achieve expected academic and socio-emotional results in preschool, avoiding school failures and behavioural problems at the beginning of primary education.

In this way, RtI is an ideal opportunity for inclusively improving education for all students, both with and without neurodevelopmental disorders, through the use of innovative approaches as VR and adaptive and motivating strategies.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 1027-1038

DOI: 10.5498/wjp.v11.i11.1027

ISSN 2220-3206 (online)

MINIREVIEWS

How non-rapid eye movement sleep and Alzheimer pathology are linked

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Author contributions: Falter A performed the literature study; Van Den Bossche MJA planned and coordinated the review and supervised the literature study; Falter A and Van Den Bossche MJA wrote the manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that there is no conflict of interest for this article.

Supported by the Funds Malou Malou, Perano, Georgette Paulus, JMJS Breugelmans and Gabrielle, François and Christian, Managed by the King Baudouin Foundation of Belgium, No. 2021-J1990130-222081.

Country/Territory of origin: Belgium

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

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Abstract

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by the presence of senile plaques and neurofibrillary tangles. Research attempts to identify characteristic factors that are associated with the presence of the AD pathology on the one hand and that increase the risk of developing AD on the other. Changes in non-rapid eye movement (NREM) sleep may meet both requirements for various reasons. First, NREM-sleep is important for optimal memory function. In addition, studies report that the presence of AD pathology is associated with NREM-sleep changes. Finally, more and more results appear to suggest that sleep problems are not only a symptom of AD but can also increase the risk of AD. Several of these studies suggest that it is primarily a lack of NREM-sleep that is responsible for this increased risk. However, the majority investigated sleep only through subjective reporting, as a result of which NREM-sleep could not be analyzed separately. The aim of this literature study is therefore to present the results of the studies that relate the AD pathology and NREM-sleep (registered by electroencephalography). Furthermore, we try to evaluate whether NREM-sleep analysis could be used to support the diagnosis of AD and whether NREM-sleep deficiency could be a causal factor in the development of AD.

Key Words: Alzheimer's disease; Mild cognitive impairment; Sleep; Non-rapid eye movement sleep; Amyloid beta-peptides; Tau proteins; Electroencephalography

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Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: February 24, 2021
Peer-review started: February 24, 2021
First decision: July 15, 2021
Revised: July 28, 2021
Accepted: August 17, 2021
Article in press: August 17, 2021
Published online: November 19, 2021

P-Reviewer: Moon SW
S-Editor: Gong SS
L-Editor: Webster JR
P-Editor: Ma YJ



Core Tip: Non-rapid eye movement (NREM)-sleep has been shown to be important for memory consolidation. Sleep problems are not only a symptom of Alzheimer's disease (AD) but also seem to increase the risk of developing AD. We herein present the results of studies that investigated the relationship between AD pathology and NREM-sleep (registered by electroencephalography). We discuss whether the presence of AD pathology is associated with specific changes in NREM-sleep on the one hand and whether these changes can serve as an aid in diagnosing the disorder on the other. We also evaluate whether a lack of NREM-sleep may play a causative role in the development of AD.

Citation: Falter A, Van Den Bossche MJA. How non-rapid eye movement sleep and Alzheimer pathology are linked. *World J Psychiatr* 2021; 11(11): 1027-1038
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1027.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1027

INTRODUCTION

Alzheimer's disease

Worldwide, approximately 50 million people suffer from dementia. The most common cause of dementia is Alzheimer's disease (AD)[1]. The number of people affected by this neurodegenerative disease is increasing every year. The WHO considers AD as a priority because it is one of the major causes of morbidity and mortality in the aging population.

Pathogenesis

The two main pathological abnormalities found in AD are amyloid plaques and neurofibrillary tangles. Familial forms of AD exist in which hereditary mutations lead to the development of the disease. However, sporadic occurrence is much more common. Amyloid plaques accumulate extracellularly. They are largely composed of amyloid-beta-42 (Aβ42) and to a lesser extent of amyloid-beta 40 (Aβ40), both products of amyloid precursor protein (APP) metabolism. Aβ42 is less soluble than Aβ40. Generally, they are first detected in the neocortex. The subcortical structures are affected at a later stage[2,3]. The neurofibrillary tangles consist of paired phosphorylated tau-helices. These tangles accumulate in the neuronal cytoplasm and this damages the neurons. In contrast to plaques, the accumulation of neurofibrillary tangles is more predictable. Tau pathology typically begins in the medial temporal lobe allocortex (MTL; consisting of the hippocampal region, perirhinal, entorhinal, and parahippocampal cortices), where amyloid plaques accumulate less frequently, and then spread to the associative neocortex. Neuronal loss and synaptic damage usually develop after the tangles have formed[2].

Although now sometimes challenged, the most accepted hypothesis is still that the disease process is triggered by an increased production of the pathological Aβ peptides from APP by β- and γ-secretase, and by a reduced elimination of these pathological peptides (the amyloid hypothesis). According to this hypothesis, tangle formation and neuronal dysfunction follow downstream of the plaques. However, there is a strong association between the clinical symptoms, neurodegeneration and the tangles, and tau can also induce neurodegeneration independently of Aβ. It could therefore also be possible that tau and Aβ exert their effect *via* other pathways and amplify each other's harmful effects[4]. Both seem essential in the pathogenesis of AD, but it is still unclear how they precisely affect each other. While the current hypothesis is that the accumulation of these proteins is causally related to synaptic and neuronal loss in the brain, AD is considered a complex and multifactorial disorder, in which both genetic and environmental factors affect the development and course of the disease[4].

Clinical manifestations

Progressive problems with episodic memory are usually the first complaint of AD patients. In an early stage, mainly short-term memory is involved. However, as AD progresses, other cognitive domains are also affected. Often topographic disori-

entation, problems with word-finding, sentence comprehension and behavioral problems will follow[2]. When there is an objective memory impairment without affecting the other cognitive domains and with a limited impact on daily functioning, this is called amnestic mild cognitive impairment (aMCI). This is seen as an intermediate stage, as individuals with aMCI have a strong increased risk of progressing to AD[5].

Although memory complaints are usually the first symptom that alerts both the environment and the patient to AD, sleep problems often precede these by several years. However, problems with sleep without the presence of memory complaints are often not immediately associated with AD. As the disease progresses, the severity of these sleep problems grows, and this is accompanied by a major impact on the quality of life of both the patient and the people around.

In addition, sleep problems are no longer only considered to be a major symptom of AD, but also a factor that may adversely affect the pathogenesis and symptomatology of this neurodegenerative disease. Episodic memory impairment is indeed the main characteristic of AD, but sleep, independent of AD, is essential for the optimal functioning of this cognitive domain.

Non-rapid eye movement-sleep

Sleep, based on electroencephalogram (EEG) oscillations, is divided into non-rapid eye movement (NREM)1-, NREM2-, NREM3- and REM-sleep. During a sleep cycle, different phases occur. One night has multiple cycles. Two characteristics of REM-sleep are low amplitude desynchronized fast waves and muscle atony. NREM1 is a short transition phase between awake and sleep in which alpha waves (10-15 Hz) decrease while theta waves (4-8 Hz) become predominant. Sleep spindles (11-15 Hz) and K-complexes (KC; < 1 Hz) that occur on a background of theta waves are typical of NREM2. Spindles (11-15 Hz) are generated in the thalamus and synchronized by thalamo-cortical interactions[6,7]. KC are thought to protect sleep from external stimuli. During NREM3 (also called slow-wave sleep; SWS), delta waves, waves with low frequency (0.5-4 Hz) and high amplitude, are predominant along with slow oscillations (SO), slow waves (< 1.25 Hz) with high amplitude[8]. The activity of delta waves and SO together is sometimes called slow-wave activity (SWA). The SO arise from the superficial layers of the frontal cortex. Spindles are also present during NREM3. Sharp wave ripples (SWR) (80-140 Hz), which can be described as flares of synchronized neuronal activity in the hippocampus, are a third feature of NREM3.

For storing information in the long-term memory, NREM-sleep in particular seems to be important. To ensure a transfer of information, the neurons that represent a specific memory in the hippocampus are repeatedly activated. If the neocortex is activated simultaneously, the transfer of information takes place[9]. This co-activation gives the slow-learning cortex the opportunity to integrate the new information into the long-term memory. This happens mainly during NREM3. Especially SWR, spindles and SO appear to be essential for this process. A recent study[10] concluded that it is the exact timing and precise coupling of SWR, spindles and SO that ensure the transfer of information from the hippocampus to the cortex. The SWR precedes the spindle and activates the neuronal sequence associated with a recent memory. The spindles and the subsequent cortical SO help process this memory. The timing of these events determines the quality of the information transfer that takes place during the SWS[8].

NREM-sleep, normal aging and AD

Aging is associated with physiological changes in sleep patterns. In general, older people sleep less, go to bed earlier, get up earlier, sleep more during the day, wake up more at night and have difficulties in falling asleep again[11]. Age-related changes in the oscillations can also be observed on the EEG. Both the quantity and quality of NREM3 decreases while the length of NREM1 in particular and to a lesser extent NREM2 increases[12]. Older people have a decreased percentage of SWA and the amplitude is on average lower compared to younger people. This difference is most pronounced in the frontal brain regions where the SWA originates[13]. The density, duration and peak and mean amplitude of sleep spindles also decrease with aging[14, 15].

As early initiation of therapy usually yields better results, attempts have been made to identify symptoms that are specific to AD and that can be measured early in the course of the disease. The previous paragraph indicates that sleep quantity and quality decreases with aging even in the absence of neurodegenerative pathology, and are therefore not unique to AD. Nevertheless, interest in sleep in AD has increased rapidly in recent years. This is because, on the one hand, specific sleep problems such as

excessive daytime sleepiness and insomnia are more prevalent in AD. On the other hand, these sleep problems, similar to the formation of senile plaques and neurofibrillary tangles, seem to appear several years before the cognitive decline. As AD is considered a multifactorial disease, another focus of current research is identifying risk factors. Sleep deprivation (SD; no sleep for one night) and Alzheimer's pathology such as senile plaques and neurofibrillary tangles have been shown to be associated. Thus, there may be a bi-directional relationship between sleep problems and AD.

As NREM-sleep is of great importance for proper functioning of episodic memory, which is also the cognitive domain that often deteriorates first in AD, several studies have concluded that NREM-sleep in particular is responsible for the association found between AD-pathology and sleep. However, the majority of the studies on this topic analyzed sleep through subjective reporting and did not differentiate between the different sleep stages. The purpose of this literature review is therefore to provide an overview of the literature investigating the relationship between NREM-sleep and AD in humans. In addition, studies will be discussed that specifically investigated the relationship between AD-pathology (in particular amyloid and tau) and NREM-sleep and which analyzed the possible causative role of NREM-sleep in the pathogenesis of AD. Subsequently, we briefly review the experiments that investigated whether NREM-sleep might be one of the pathways through which AD-pathology affects memory. Finally, based on the results found, it is discussed whether measuring NREM-sleep *via* EEG could in the future be used in the prevention, diagnosis and treatment of AD.

SEARCH METHODS

We performed a search of the literature using the PubMed, Embase and Cochrane Library databases. The search terms used at the start of the literature study were "Alzheimer's disease" AND "NREM" OR "non-rapid eye movement" OR "nonREM" OR "SWS" OR "slow-wave".

English-language studies in which human sleep was objectively measured by EEG and which included aMCI or AD as the study population were included. Studies analyzing the sleep of subjects without cognitive impairment were included only if the purpose of these studies was to gain more insight into the association between AD and NREM-sleep, and if amyloid-beta or tau measurements were compared with NREM-EEG data. The references of the above articles were also searched for additional articles that met the inclusion criteria.

RESULTS

One hundred and twenty-nine individual studies were found and screened, of which 31 met our inclusion criteria. An overview of the article selection is shown schematically in Figure 1. The results found are further described below.

NREM-sleep changes in AD and aMCI cognitive impairment

Prinz *et al*[16] and Vitiello *et al*[17] were among the first to detect that the percentage of NREM (duration NREM/duration total sleep) was significantly lower in AD patients than in elderly with intact cognition (EIC). More recent studies[6,18,19] also confirmed that people suffering from AD have a lower percentage of NREM3 compared to EIC. In several studies[6,18,20,21], a smaller percentage of NREM-sleep was associated with lower MMSE scores, not only in the total study group but also within the AD group. As diagnostic markers that can contribute to early identification of AD are sought after, Westerberg *et al*[22] studied NREM in aMCI patients. They found that the percentage of NREM3 was less in the aMCI group than in EIC. Within this aMCI group, patients with a lower percentage of NREM-sleep scored worse on a test in which they were asked to reproduce in the morning what they had studied the night before[22]. Although the mean percentage of NREM3-sleep in aMCI patients in another study[19] was lower than in the EIC group, this difference was not significant. This study by Gorgoni *et al*[19] also included AD patients and they found a significant difference in NREM3-sleep percentage between AD patients and EIC. The findings by Reda *et al*[20] were similar: The difference in percentage of NREM3 was not significant between aMCI and AD, but significant between AD and the EIC group. In contrast to Gorgoni *et al*[19], the difference between aMCI and the EIC group in this study did

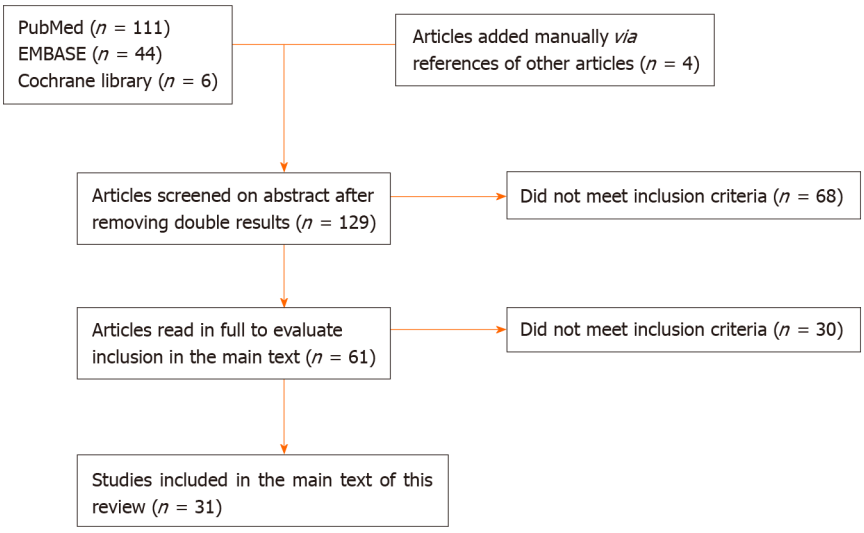


Figure 1 Schematic overview of article selection.

however reach the significance level[20]. A smaller study[23], where we have to be careful when interpreting the results due to the heterogeneity of the different types of dementia that were included, analyzed the SWA within the 0.4-3.6 Hz range, the activity that predominates during NREM3 sleep. A shift was found within this frequency spectrum in patients with dementia. There was a significant decrease in the percentage and incidence of delta waves with a frequency less than 1.6 Hz in the group with dementia. At the same time, there was a significant increase in the incidence of delta waves with a frequency higher than 2 Hz[23].

Many functions of NREM-sleep and its microstructures are not yet known. What is known is that SWR, SO, spindles and KC, that mainly occur during NREM-sleep, are important for our memory function. Therefore, these microstructures of NREM-sleep were also investigated in patients with aMCI or AD. Rauchs *et al*[14] hypothesized that patients with AD would have fewer spindles compared to EIC, but this difference was not significant. In a more in-depth analysis whereby a distinction was made between fast (13-15 Hz) and slow (11-13 Hz) spindles[9], only the amount of fast spindles was significantly reduced in AD patients[14]. Westerberg *et al*[22] made a distinction based on location, and studied the spindles separately in a parietal and a frontal lead, where the fast and slow spindles, respectively, are most pronounced[7]. They noted a significant reduction in the aMCI group of the fast spindles in the frontal but not in the parietal lead. For the slow spindles, there was no difference in both leads[22]. The reduction of fast spindles was confirmed by Gorgoni *et al*[19]. They found a significant reduction in density (spindle number/length NREM sleep) of all spindles and of the fast spindles registered *via* the parietal lead in aMCI and AD, while the slow spindles did not differ. There was no difference between aMCI and AD[19]. A recent study[18] analyzed the total amount of spindles during NREM-sleep. The density, amplitude and duration of these spindles were lower in AD than in aMCI and EIC. They were also lower in aMCI compared to EIC. Fast spindle density and spindle amplitude were both positively correlated with the MMSE scores[18]. Within the aMCI and AD subgroups, the occurrence of the spindles was positively correlated with the performance on a memory test in which the studied material was examined in the morning[19,22].

De Gennaro *et al*[6] also analyzed the KC. AD patients had a drastic decrease (40%) in KC-density during NREM-sleep. This decrease was most pronounced in the frontal lead[6]. Reda *et al*[20] reported similar observations. Patients with AD had a lower KC-density. The density was significantly less not only compared with EIC, but also with the aMCI group. The difference was not significant between aMCI patients and EIC [20]. A recent study[18] measured the frontal KC-density in EIC, aMCI and AD. There was no significant difference in density between EIC and aMCI, while the density and amplitude were significantly lower in AD. Only the KC-amplitude differed between aMCI and EIC. No difference was found within the three groups in the duration of the KC[18]. The first prospective cohort study[24] on KC-complexes in aMCI confirms most of these results. In this study, the sleep of both aMCI and EIC was recorded after specific time intervals during a follow-up period of 2 years. Subjects who developed AD and subjects whose aMCI status remained stable during two years of follow-up,

were in the analysis divided in a progressive aMCI group (pMCI) and a stable aMCI group (sMCI), respectively. The KC-density at baseline and at 6 mo did not significantly differ among the three groups. In contrast, the KC-amplitude was significantly lower in sMCI and pMCI compared with EIC, while there was no difference between sMCI and pMCI subjects. At 12 and 24 mo, the KC-density and KC-amplitude was higher in EIC compared with sMCI and pMCI, but was also higher in sMCI than in pMCI. At 12 mo, when the pMCI subjects did not yet meet the criteria of AD, the KC-density and KC-amplitude was nevertheless already significantly lower in pMCI than in sMCI. The KC-density correlated positively with the MMSE scores in all studies[6,18,24].

The link between NREM-sleep and Aβ and tau

Aβ42 and tau are pivotal in the pathogenesis of AD. Therefore, it was also investigated whether specific NREM EEG-abnormalities could reflect the presymptomatic presence of Aβ and tau in the cerebrospinal fluid (CSF) or on imaging.

Aβ- and tau-specific positron emission tomography scans and the NREM-sleep EEG

Mander *et al*[25] detected a relationship between Aβ deposition in the medial prefrontal cortex and a reduction in NREM3 in EIC. A detailed analysis showed that this association was due to an underlying association between Aβ and less activity in the 0.6-1 Hz range. This inverse relationship was strongest between Aβ in the medial prefrontal cortex and sleep recorded *via* the frontal EEG lead. There was no significant association with the total 1-4 Hz frequency spectrum[25].

Lucey *et al*[26] analyzed not only Aβ but also tau presence on the brain scans of older adults who were predominantly cognitively intact (some subjects with aMCI). The percentage of 1-4 Hz-SWA decreased when more Aβ and tau were seen on imaging. For Aβ, there was an inverse association between Aβ deposition in the frontal, temporal and parietal cortices and both the 1-2 Hz and 1-4 Hz activity. The total amount of tau, and tau at the level of the entorhinal, parahippocampal and inferior temporal areas, was in these regions most strongly associated with the 1-2 Hz activity. The associations found with tau were much stronger than those with Aβ, and the associations with Aβ disappeared after statistical correction for multiple testing [26]. In both studies[25,26], the associations found remained significant when corrected for cortical thickness. Winer *et al*[10] tried to determine whether there are EEG abnormalities that are only associated with Aβ and not with tau and vice versa. The MTL and the cortex were analyzed because these regions are particularly susceptible to tau- and Aβ-damage in AD, respectively[2]. They observed that a weaker coupling between SO and spindles was associated with more accumulation of tau in the MTL [10]. There was no association between the strength of the coupling and cortical Aβ. However, for Aβ, they found, in line with the results of Mander *et al*[25], a significant inverse correlation between cortical Aβ and activity in the 0–6-1 HZ range[10]. A reduction in 0.6-1 Hz-SWA predicted a higher amount of cortical Aβ. MTL-tau had no significant association with this frequency interval or with any other subgroup frequency of the 0.6-4 Hz range[10]. A new study of Winer *et al*[27] aimed to address the lack of longitudinal data on this topic. The sleep of EIC was registered during one night in the beginning of the study. Around the same time positron emission tomography (PET) scans were taken in order to analyze Aβ accumulation. During a follow-up period of on average 3.7 years, multiple follow-up PET scans were performed to measure the change in Aβ. They found a negative correlation between the proportion of 0.6-1 Hz SWA at baseline and the change in Aβ during the follow-up. This negative correlation was frequency range specific, as they did not find an association between total SWA (0.8-4.6 Hz) and Aβ change. In addition, the strength of SO-spindle coupling was not associated with the rate of Aβ change[27].

Aβ- and tau-CSF concentrations and the NREM-sleep-EEG

Lucey *et al*[26] observed no correlation between CSF-Aβ42 and total NREM-SWA while using a similar study design where imaging was replaced by CSF analysis. In this study[26], there was however a significant inverse relationship between the 1-4.5 Hz-SWA and the ratio between CSF-tau and CSF-Aβ42 (CSF-tau/CSF-Aβ42). The ratio between phosphorylated tau and CSF-Aβ42 (CSF-p-tau/CSF-Aβ42) was also analyzed separately and this relationship was also significant. The inverse relationship between CSF-tau/CSF-Aβ42 and the 1-2 Hz SWA was the strongest. Kam *et al*[28] explored associations with the microstructural features of NREM-sleep. A decrease in spindle density during NREM2 was correlated with an increase in CSF-tau and CSF-tau/Aβ42 in EIC. This relationship was strongest between specifically CSF-tau and fast spindle

density, while there was no relationship with the slow spindles. Frontally recorded 0.5-4 Hz-SWA was also inversely related with CSF-Aβ42 but not with CSF-tau[28]. In another study[29], CSF-Aβ42 was inversely related with the duration and percentage of NREM3, while there was no significant relationship between CSF-Aβ42, total sleep length and the length of the other sleep stages. Additionally, no association was found between the percentage of NREM3 and CSF-tau[29]. In mild and more advanced AD patients, there was only a correlation between CSF-tau and a decreased percentage of NREM3; this association did not apply to CSF-Aβ42 and the percentage of NREM3[21].

The impact of a NREM-sleep deficit on CSF-Aβ and CSF-tau

Several studies[30,31] have reported that CSF-Aβ fluctuates over the course of a 24-h period, with the highest concentration being measured in the evening and the lowest in the morning after sleep. Following this finding, and with the aim of gaining more insight into the relationship between NREM sleep and AD pathology, the effect of sleep deprivation (SD) on the CSF-Aβ and CSF-tau concentrations of adults with intact cognition were examined. Lumbar catheters were used in two studies[32,33] to frequently monitor CSF levels during both normal sleep and SD. In the study of Ooms *et al*[32] CSF-Aβ42 decreased significantly (6%) after sleep, while the concentration did not decrease after SD. Neither sleep nor SD significantly affected CSF-tau. Lucey *et al* [33] found a similar but greater increase (30%) in CSF-Aβ after SD and, in contrast to Ooms *et al*[32], also noted an increase in CSF-tau (50%). Shokri *et al*[34] conducted their study assuming that radio tracers also identify soluble amyloid and therefore can show a direct increase in Aβ42 on imaging. They compared two scans of the same EIC that were taken after one night of normal sleep and after one night without sleep. SD resulted in a significant increase in Aβ42 in the right hippocampus, parahippocampus and thalamus on the second scan[34]. In an attempt to determine whether NREM3 specifically contributes to this decrease in CSF-Aβ following sleep, Ju *et al*[35] disrupted sleep only during NREM3. This intervention logically resulted in a reduced percentage of SWA and a reduced total sleep duration. The percentage of NREM1 increased, while the other sleep variables remained unchanged. After NREM3 sleep disturbance, CSF-Aβ40 increased. There was no significant association between CSF-Aβ40 and CSF-Aβ42 and NREM, REM, or total sleep length. No correlation was found between NREM3 disturbance and CSF-tau concentrations[35]. Olsson *et al*[36] wanted to address the lack of knowledge on the chronic effects of SD on AD markers by allowing subjects with intact cognition to sleep only partially (max. 4 h) in their sleep laboratory for five consecutive nights. In the same subjects, physiological sleep was also monitored during five other nights. There was an interval of one month between both circumstances. After the completion of each period, a lumbar puncture was performed. Their hypothesis was that five nights of partial sleep deprivation (PSD) would lead to increased CSF-Aβ or CSF-tau. However, they found no significant difference in CSF-Aβ40, CSF-Aβ42 or CSF-tau concentrations between the two conditions. EEG analysis showed that despite the shorter total sleep time (207 min) in PSD, there was no significant difference in NREM3 (4 min) length. The lengths of NREM1, NREM2 and REM were shorter with PSD (19 min, 131 min and 52 min, respectively)[36].

The link between Aβ and tau, memory and NREM-sleep

Episodic memory impairment is characteristic of AD. As NREM-sleep is important for this cognitive domain, research groups have attempted to investigate whether NREM-sleep is still important for memory function, when AD pathology is already present in the brain.

In the previously mentioned studies[14,19,22], there was in the total study population (EIC, aMCI and AD) a proportional relationship between the results on memory tests or MMSE scores and, among other things, the percentage of NREM3-sleep, the spindle density and the KC-density. Furthermore, this association persisted when aMCI and AD were considered separately. Liu *et al*[18] detected in their study the strongest associations between NREM3 percentage and MMSE, and between KC-density and MMSE. These results are based on experiments in which the physiological sleep of aMCI, AD and EIC was measured *via* EEG during one night. A recent study [37] did more than just record physiological sleep. It used an intervention to investigate the link between NREM sleep, memory and AD. aMCI patients in this study had to study information before they went to sleep. The following night their SWA was stimulated *via* acoustic stimulation. The same experiment was repeated but without stimulation during sleep. The first observation was that acoustic stimulation significantly increased SWA. The second one was that on average aMCI patients remembered more after a night of stimulation, although the difference did not reach

significance[37]. The research group that previously detected the inverse correlation between cortical Aβ and SWA, also used memory tests in their experiments[25]. Their hypothesis was that cortical Aβ indirectly, by reducing NREM-SWA, leads to less information stored in the cortex. Decreased SWA was in this study[25] associated with less hippocampal-cortical information transfer during NREM-sleep. Statistical analysis (structural equation models) showed that the association between cortical Aβ and impaired memory was dependent on the degree to which the 0.6-1 HZ-SWA decreased as an intermediate factor. Cortical Aβ and memory were only significantly inversely related in the statistical model in which NREM-SWA was included[25].

DISCUSSION

This review shows that there is an association between AD and NREM-sleep. The number of EEG studies examining this association is rather limited up to now, but current results suggest that NREM-sleep analysis could in the future be useful in the diagnosis, prevention and therapy of AD.

Some sleep problems, such as excessive daytime sleepiness and insomnia, are characteristic of AD. The studies discussed suggest that certain specific changes in NREM-sleep could help in the diagnosis of aMCI and AD. Based on the current literature, a decrease in the NREM3 percentage should be able to differentiate persons with AD or aMCI from EIC. Although in each study this percentage was lower in AD compared to aMCI, the difference was not always statistically significant. Nevertheless, this suggests that the percentage might decrease progressively during the course of the disease. Some microstructural properties of NREM-sleep were also found to be significantly different in AD. A reduction in fast spindle density, amplitude and duration could help to identify aMCI and AD patients. While the spindle density could not distinguish the aMCI group from the AD group in the study by Gorgoni *et al*[19], Liu *et al*[18] showed a difference in both density and amplitude between both groups. Measuring spindles and NREM3 percentage with EEG could therefore assist in diagnosis at an early stage. In contrast, KC-density was consistently lower in AD compared to the aMCI group. This parameter might therefore be especially useful at a later stage, as in the majority of experiments the KC-density was not different between aMCI and EIC. A reduction in KC-amplitude may occur earlier and might be useful in distinguishing aMCI from EIC[24].

An association between sleep and AD pathology has been demonstrated before. Aβ and tau were associated with less qualitative sleep in humans[38]. However, the majority of these studies evaluated sleep subjectively and therefore could not differentiate between the different sleep stages. The discussed results suggest that AD pathology may cause EEG abnormalities particularly in NREM-sleep. The *in vivo* measurement of Aβ and tau *via* brain imaging is used in the clinic to support the diagnosis of AD. Pathological abnormalities on imaging characteristic of AD co-occurred with specific EEG abnormalities during NREM-sleep in the reviewed studies. A reduced percentage of 0.6-1 Hz-SWA reflected increased cortical Aβ in both Winer *et al*[10] and Mander *et al*[25], while there was no association with tau. Due to technical limitations, Lucey *et al*[26] did not analyze below 1 Hz, so they could neither confirm nor refute these results. In contrast, less than 1-2 Hz SWA could indicate tau pathology in the MTL and the orbitofrontal, inferior parietal and inferior temporal cortex[26]. Winer *et al*[10] did not confirm this association between tau and SWA, but identified a microstructural feature specifically associated with tau. The SO-spindle-coupling, and in particular the progressive loss of coupling intensity, might identify individuals with high MTL-tau earlier. The on average older population in the study by Lucey *et al*[26] could possibly explain the fact that they did detect an association between tau and SWA. As mentioned in the introduction, tau indeed first accumulates in the MTL and only later spreads to the cortical areas where the slow waves are generated.

An increase in the ratio of CSF-tau/CSF-Aβ42, CSF-tau, and a decrease in CSF-Aβ are also used in the clinic as biomarkers to support the diagnosis of AD[2]. A preclinical rise in CSF-tau reflects an increased risk of AD. Although there is more debate about the predictive value of CSF-Aβ, the literature suggests that CSF-Aβ increases in a preclinical stage which promotes plaque formation and decreases at a later stage only when plaques are more numerous[39]. These CSF biomarkers were also associated with NREM abnormalities in EIC. Reduced fast spindle density during NREM2 and 1-2 Hz-SWA were associated with an increase in CSF-p-tau, CSF-tau and CSF-tau/CSF-Aβ42[26,28]. CSF-tau and CSF-p-tau are markers of neuronal damage and neurofibrillary tangles, respectively[40]. These NREM changes could potentially

be an early indicator of tau pathology. The results for amyloid were less consistent. Kam *et al*[28] and Varga *et al*[29] reported an inverse association between the percentage of NREM3 and CSF-Aβ42. Lucey *et al*[26] could not confirm this association. Again, their study population could have some influence on the results, as there were also aMCI patients in this study, and the presence of plaques might reduce CSF-Aβ fluctuations. Hence, EEG measurements, like CSF-analysis and imaging, could be used to support the diagnosis of AD and to identify individuals at increased risk in a non-invasive way. More research is needed however, to both confirm the results discussed and to quantify these abnormalities into clinically useful parameters.

Measuring NREM-sleep might have even more clinical potential. It has been acknowledged for some time that chronic sleep problems entail an increased risk of developing AD. For example, the risk that adults with intact cognition but with untreated obstructive sleep apnea hypopnea syndrome or insomnia will develop AD later on is higher than in persons without a sleep disorder[41-43]. Over the last decade, evidence is mounting that a lack of NREM3-sleep may be an important cause of this increased risk, and that NREM3 may play a causal role in the pathogenesis of AD. However, the design of the above-mentioned studies usually did not allow determination of the causality in the association found between CSF concentrations or imaging and NREM-sleep abnormalities. Additional arguments that sleep problems could potentially lead to Alzheimer's pathology are found in studies in which participants are exposed to acute SD. All SD studies[32,33,35] discussed reported a CSF-Aβ concentration that was higher after SD than after normal sleep. For tau, the effects were less consistent. In the majority of studies, no nocturnal change in CSF-tau was observed in either physiological sleep or SD. Only one study found a significant increase in CSF tau after SD[33]. One possible way in which a lack of NREM3 sleep could lead to a rise in certain concentrations in the CSF is through the so-called "glymphatic system"[44]. This perivascular network, found in animal models, promotes the elimination of soluble proteins, including Aβ, from the central nervous system. The glymphatic system is mainly active during sleep and its function is said to be maximal during SWS[45]. The findings of Ju *et al*[35] that a selective disruption of SWA was inversely correlated with an increase in CSF amyloid, and that there was no association with total sleep or REM sleep, are in line with this. The selective interruption of NREM3-sleep had no effect on CSF tau. This could possibly be due to the longer half-life of tau, which means that one night without sleep has a lesser effect on the clearance of tau[46]. On the other hand, it is also possible that sleep has a different effect on the clearance of Aβ and tau. The fact that NREM3-sleep was ensured with PSD and that PSD did not induce an increase in CSF-Aβ42 or CSF-tau also supports the hypothesis that it is NREM3 that mainly affects CSF concentrations[36]. Although it seems likely that there is an increased clearance of CSF-Aβ42 during NREM3, an increased synthesis, as suggested by Lucey *et al*[26], could also be partly responsible for an increase in CSF-Aβ42 after SD. A combination of reduced clearance and increased synthesis of CSF-AB42 during SD is also possible.

Studies on humans, combining EEG recording, CSF measurements and imaging over a long period of time are needed to gain more insight into the effect of NREM-sleep on Aβ and tau and to determine whether the CSF fluctuations are due to increased clearance or to increased synthesis of these proteins. Despite the lack of clear understanding about the mechanism, ensuring NREM-sleep could become important in the prevention of AD. In addition, stimulation of SWS could be used to normalize CSF-Aβ and in this way reduce the risk of plaques. SWS stimulation also has potential as a treatment for the memory symptoms that characterize AD[37]. Problems with the transfer of information to long-term memory are namely one of the first complaints of AD. NREM-sleep and the interaction of SO, spindles and SWR play an important role in this information transfer[8]. Acoustic stimulation during SWA has previously been shown to improve memory tests in individuals with intact cognition[47]. SWS stimulation was also able to improve memory in aMCI patients[37].

The hypothesis of Mander *et al*[25] that a reduction in SWA is one of the mechanisms by which cortical Aβ impedes the storage of information in the long-term memory, could provide a possible explanation for the observation that, despite the presence of AD pathology in an aMCI stage, SWA stimulation still had a positive effect on memory. This may explain why the decline of hippocampus-dependent memory is usually one of the first symptoms of AD, while Aβ usually does not accumulate at the hippocampus until later in the disease process. There is moreover a similarity between the regions that generate NREM-SWA and the cortical areas where Aβ usually first accumulates[48]. A similar EEG study has not yet been performed in aMCI patients. However, two recent studies[49,50] in a heterogeneous group of elderly (EIC, aMCI and AD) also suggested that sleep at an early stage may partly influence the impact of

cortical Aβ on memory, as the inverse relation between cortical Aβ on imaging and memory was statistically dependent on sleep continuity as an intermediate factor. Interestingly, EIC with high cortical Aβ had a more continuous sleep in this study than the EIC with little Aβ, which might be indicative of a possible protective role of sleep on cognition in the presence of high Aβ accumulation[49,50]. These studies all focused on Aβ. Whether NREM-sleep disturbance is also one of the pathways through which tau affects memory is not yet known.

Qualitative NREM3-sleep seems to be essential for memory in both EIC and AD patients. Enhancement of SWA, such as by acoustic stimulation, might therefore be a potential therapy for memory problems in AD patients.

CONCLUSION

This review discussed the studies that examined the link between NREM-sleep and AD. Based on the presented results, examining NREM-sleep could be a new diagnostic tool for detecting aMCI and AD in a non-invasive way. Enhancement of NREM-sleep could be an exciting new option in the prevention and treatment of AD. Prospective and longitudinal studies that combine EEG measurements with imaging and CSF analyses are needed to gain more insight into the causality and the underlying mechanisms of this relationship.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 1039-1052

DOI: 10.5498/wjp.v11.i11.1039

ISSN 2220-3206 (online)

MINIREVIEWS

Empirically supported psychological treatments: The challenges of comorbid psychiatric and behavioral disorders in people with intellectual disability

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Author contributions: Gómez LE wrote the draft; Navas P, Verdugo MÁ and Tassé MJ reviewed the draft and contributed equally to this work.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Supported by Ministry of Science, Innovation and Universities, and the State Research Agency, No. PID2019-105737RB-I00/AEI/10.13039/501100011033.

Country/Territory of origin: Spain

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an

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Abstract

This paper reviews the current state of knowledge on psychological interventions with empirical evidence of efficacy in treating common psychiatric and behavioral disorders in people with intellectual disability (ID) at all stages of their life. We begin with a brief presentation of what is meant by psychiatric and behavioral disorders in this population, along with an explanation of some of the factors that contribute to the increased psychosocial vulnerability of this group to present with these problems. We then conduct a review of empirically supported psychological therapies used to treat psychiatric and behavioral disorders in people with ID. The review is structured around the three generations of therapies: Applied behavior analysis (*e.g.*, positive behavior support), cognitive behavioral therapies (*e.g.*, mindfulness-based cognitive therapy), and contextual therapies (*e.g.*, dialectical behavior therapy). We conclude with some recommendations for professional practice in the fields of ID and psychiatry.

Key Words: Behavior disorder; Intellectual disability; Psychiatry; Applied behavior analysis; Cognitive behavioral therapies; Contextual therapies

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Received: March 9, 2021
Peer-review started: March 9, 2021
First decision: July 15, 2021
Revised: July 17, 2021
Accepted: October 18, 2021
Article in press: October 18, 2021
Published online: November 19, 2021

P-Reviewer: Wang D
S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC



Core Tip: Psychiatric and behavioral disorders are more common in people with intellectual disability (ID) than in the population without ID. Although there is some consensus that empirically supported psychological treatments for psychiatric disorders in the general population can be adapted for people with ID, there is scant published evidence about their application in this population. We discuss the empirical evidence for the application of psychological treatments in people with ID. Our review is structured around the first-, second- and third-generation therapies.

Citation: Gómez LE, Navas P, Verdugo MÁ, Tassé MJ. Empirically supported psychological treatments: The challenges of comorbid psychiatric and behavioral disorders in people with intellectual disability. *World J Psychiatr* 2021; 11(11): 1039-1052
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1039.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1039

INTRODUCTION

Despite the significant challenges in establishing an accurate figure, it is estimated that approximately 1% of the population has some form of intellectual disability (ID)[1]. The causes of ID can be extremely varied, ranging from genetic alterations (*e.g.*, chromosomal or single gene alterations) that are often associated with more severe forms of ID, to environmental factors (*e.g.*, nutritional deficiencies, extreme social deprivation, or child abuse) that are often linked to milder forms.

Whatever the cause, the recommendation when defining ID is to adopt a biopsychosocial approach in which disability is conceived as the interaction of the person with their context[2,3]. Environments can therefore be more or less facilitating, and as a result, attenuate or accentuate the disability depending on existing barriers and supports. ID is a neurodevelopmental disorder whose diagnostic criteria can be found in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5)[4] and the 11th edition of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-11)[5]. It is characterized by significant limitations in intellectual functioning and adaptive behavior that appear before the age of 22 years [6].

For most of the disorders in these manuals, the diagnosis of a mental disorder relies on clinical judgment. To diagnose ID, clinical judgment is also important in the selection, administration, and interpretation of standardized tests used to determine the "significance" of the limitations in the person's intellectual and adaptive functioning, which is defined as two standard deviations or more below the population mean. This article does not focus on psychological treatments for the core symptoms of ID (for an interesting review on this topic see Thurm *et al*[7]); rather, it discusses the treatment of comorbid psychiatric or behavioral disorders in people with ID, the reason being that most interventions with this population are tertiary prevention methods aimed at treating associated conditions rather than its core features. These comorbidities are in fact one of the main causes of exclusion for people with ID and one of the most frequent reasons why they are referred to mental health services.

PSYCHIATRIC AND BEHAVIORAL PROBLEMS

There is a growing body of literature on the prevalence and treatment of psychiatric and behavioral problems in people with ID[8]. Most of the studies report that such problems are common across the lifespan for this population group. Data on prevalence rise up to 49%[9], and rates are higher in people with more severe disability[10].

The range of problem behaviors exhibited is vast, the most frequent being self-injury, aggression toward others, disruptive behaviors, inappropriate sexual behaviors, stereotyped behaviors, and pica[11]. Problem behaviors may have a biological, psychological, social, or environmental etiology; or they may be the result of a combination of these factors. They may be a response to a specific social situation (*e.g.*, rejection), stress (*e.g.*, a major transition, loss of a loved one), or may appear as part

of the symptomatology of a psychiatric disorder (*e.g.*, elevated irritability or paranoid ideation associated with a psychotic disorder may lead to aggression).

Thus, problem behaviors are not defined as a diagnostic category, but are framed within a contextual, non-etiological model where the behaviors are not problematic per se. Whether they are considered to be a problem behavior depends on a number of factors, such as their characteristics (*i.e.*, frequency, duration, intensity), personal variables (*e.g.*, age), or contextual variables (*e.g.*, social norms that govern the environment in which the behavior occurs; the interpretation and meaning given to the behavior by observers). It is vitally important to understand that a problem behavior serves a function; the responsibility of professionals is first-and-foremost to find out what the person wants or needs (*e.g.*, attention, tangible), trying to communicate (*e.g.*, pain, discomfort), or trying to escape (*e.g.*, demand or situation), which will then allow them to design and implement an intervention that responds to the function of said behavior so that the problem behavior is no longer needed[12].

Attitudes toward psychiatric disorders in people with ID have evolved over the years: first, there was outright denial (*e.g.*, until the mid-twentieth century, the possibility that this population might experience psychiatric disorders was not even recognized); there has also been a phenomenon known as diagnostic overshadowing (where the symptoms arising from physical or psychiatric disorders are misattributed to ID, leading to denied diagnosis and treatment); and, at the other extreme, it is common today to have reports of prevalence rates that double or triple those observed in the population without ID. In childhood and adolescence, for example, the most commonly reported comorbid disorders in this group are attention-deficit/hyperactivity disorder (30%), problem behaviors, autism spectrum disorder (ASD), anxiety disorders, and depressive disorders[9].

A study by Hughes-McCormack *et al*[13] confirmed ID as a predictor of psychiatric disorders [odds ratio (OR) = 7.1; 95% confidence interval (CI): 6.8-7.3], as they found a substantially higher prevalence of psychiatric disorders at all ages compared with the population without ID. The scientific literature also noted that when a diagnosis of ID is added to a diagnosis of ASD, the likelihood of other co-occurring psychiatric disorders is much higher than in the general population (OR = 130.8; 95%CI: 117.1-146.1)[14].

It is now widely accepted that people with ID experience the full range of psychiatric disorders as people without ID. The disagreement lies in whether these disorders manifest themselves (*i.e.*, signs and symptoms) in the same way or rather in an "atypical" way. As Tassé[15] pointed out, some clinicians have proposed using certain behaviors as equivalents to DSM symptoms, whereas others feel that there is lack of evidence to support behavioral equivalents. The result is a dichotomy opposing those who defend the use of conventional diagnostic systems (DSM, ICD) and those who prefer adaptations specifically developed for people with ID. Reference manuals for the latter would include, for example, the *Diagnostic Manual-Intellectual Disability* (DM-ID-2)[16] – an adaptation of the DSM-5 – and the *Diagnostic Criteria for Psychiatric Disorders for use with Adults with Learning Disabilities/Mental Retardation* (DC-LD)[17] – an adapted version of the ICD-10.

INCREASED VULNERABILITY

The prevalence rates cited above can be explained by the increased biopsychosocial vulnerability in people with ID to develop problem behaviors and psychiatric disorders. It is thus generally accepted that there is a greater biological vulnerability, which predisposes people with ID, for example, to show certain behavioral phenotypes in specific genetic syndromes, alongside the interaction of other psychological and contextual factors often unique to people with ID. We will now look at some of the factors that are commonly associated with problem behaviors and psychiatric disorders.

Health problems and difficulties accessing health services

People with ID experience more health problems than the general population. They are more frequently affected by cardiovascular diseases, obesity, diabetes, epilepsy, chronic constipation, kidney disease, osteoarticular disorders, and thyroid disorders [18]. They are also more likely to have poorer oral health[19], lower physical activity levels, higher sedentary behavior, and poorer sleep hygiene[20].

People with ID experience a number of barriers to accessing preventive health care services compared to the general population[21], to receiving routine medical care[22]

and accessing mental health services[23]. The scientific literature cites inadequate training of mental health professionals, organizational barriers, lack of services, and poor quality of services as the main obstacles to accessing appropriate mental health care[24]. Barriers are even greater for those with the most severe disabilities[25,26].

Lack of training and negative attitudes among health professionals

The attitudes of health professionals toward people with ID have a major impact on the supports and care they provide. Yet, as we have already mentioned, multiple studies have highlighted the lack of ID training among social and health care professionals[27,28], which has repercussions on the quality of emotional support they provide[29].

Among the difficulties in providing satisfactory care, professionals cite not only heavy workloads and resource constraints, but also their own feelings of insecurity, stress, frustration, embarrassment, and fear of dealing with this population[28,30,31]. Worse still, some studies have reported blatant examples of disrespect, such as making negative comments while the person is present, or completely ignoring the person with ID and addressing their companion instead[32]. It is not uncommon for health care providers to stereotype people with ID[31], to disregard this population's preferences and decisions regarding their own medical care[33], or even to deny them health care services altogether[34].

A possible explanation for these negative attitudes is that a large proportion of health care professionals are unfamiliar with the essential components that make up the daily lives of people with ID[31]. In fact, many health care professionals have never had contact with this population[30], and yet contact and interaction are precisely what is required in order to educate health care professionals about life with a disability and promote more positive attitudes.

Polypharmacy

The issue of polypharmacy in people with ID is also frequent and worrisome. Treating multiple comorbidities and the frequent secondary health problems experienced by people with ID often results in complex polypharmacological interventions, with significant health implications and a high risk of adverse side effects and interactions between medications[28], many of which often go undetected[35].

Studies tend to converge in pointing out the high use of antibiotics, antihypertensive drugs, and lipid-lowering agents, which are administered together with anticonvulsants, psychotropics, antidepressants and antipsychotics. Bowring *et al*[36] found that 71% of people with ID took some type of medication and, of these, 38% took psychotropics. In fact, it is estimated that between 22% to 72% of people with ID take antipsychotics[36,37], and up to 13% take them at doses higher than what is recommended in medication guides[35]. In many cases, the underlying reason for these high polypharmacy rates is unrelated to the presence of a diagnosed psychiatric disorder. According to Sheehan *et al*[10], 71% of people with ID using antipsychotics had no record of a diagnosed mental illness. It would therefore seem that psychotropic medication is a common treatment for psychiatric and behavioral problems in people with ID, to the detriment of other non-pharmacological approaches such as behavioral therapies or positive behavior support (PBS)[38].

The situation is all the more concerning when we consider that the evidence supporting the safety of these medications in this population is lacking because people with ID are often excluded from randomized clinical trials[39]. Given the polypharmacy that a single individual may be taking at a given time, it is impossible to ignore the potential for dependence and substance use disorder.

Changes and transitions

People with ID may be exposed to a greater number of stressful situations, which are directly (*e.g.*, health problems) or indirectly (*e.g.*, rejection and exclusion) related to their disability and impaired coping strategies. These stressors often lead to a deterioration in their emotional state, triggering emotional difficulties[40,41].

Major life events and transitions, which increase as a person ages[42], require appropriate planning that is sensitive to the person with ID and that anticipates changes in order to avoid emotional stress[43]. Yet gaps in planning occur frequently throughout their lives, whether in transition from one service to another, when they are of school age, in employment or residential settings, or at end of life. These situations contribute to a higher prevalence of depression and anxiety.

End-of-life care deserves particular attention, given the many difficulties and barriers faced by people with ID in later life stages[44]. The loss of significant others

and the (often complicated or pathological) grieving process are extremely important issues because of the contextual and emotional changes that can result from a bereavement.

Rights violations

Based on the above discussions, it will come as no surprise that people with ID are more likely to encounter stressors: these include exclusion, interpersonal loss and rejection, overprotection and infantilization, lack of family and social support, stigmatization and low expectations, and rights violations and victimization[45]. The socioeconomic disadvantage that often accompanies ID increases the risk of negative life events[46]. In this context, there is an urgent need for effective measures to facilitate the full realization of the rights enshrined in the Convention on the Rights of Persons with Disabilities (CRPD)[47]; and to ensure that people with ID do not become victims of fundamental rights violations that increases their vulnerability to emotional difficulties. The quality of life conceptual framework has proven to be a useful vehicle to facilitate this task of fulfilling the specific rights highlighted in the CRPD for this collective[48-51].

EMPIRICALLY SUPPORTED PSYCHOLOGICAL TREATMENTS

Psychological treatments with strong empirical support for efficacy and efficiency in people with ID are extremely scarce. One of the reasons to explain this paucity of empirical evidence is that most people with ID who present with problem behaviors and psychiatric disorders are not receiving appropriate psychological treatments. Although there is ample evidence showing that pharmacological interventions alone are less effective than behavioral interventions, treatment is regrettably often reduced to the use of physical (*e.g.*, exclusion), mechanical (*e.g.*, restraints), or chemical (*e.g.*, psychotropic) interventions.

Further, considerable interindividual differences mean that evidence of the efficacy of an intervention in people with a lower level of support needs may not be generalizable to people with more significant and complex support needs, and vice versa. Most research into psychological treatments has focused on people with lower levels of support needs.

It is extremely difficult to conduct randomized clinical trials and large-scale studies, as people with ID may have such significant support needs making it ethically questionable to assign them to a waitlist control group. Moreover, in this area, small differences may be clinically significant, even when they are not statistically significant.

Finally, we must not forget that there is also evidence pointing to the effectiveness of intrusive and aversive interventions that in effect pose a threat to people's rights (hence introducing an ethical quandary). Considerable effort has been devoted to demonstrating that certain interventions are shown to be ineffective, as has been the case with facilitated communication[52,53].

We concur with Campbell *et al*[54], who warned against the oversimplification of the concept of effectiveness into "what works/doesn't work", and instead they recommended looking at what interventions work for whom, when, where, and how, assessing their appropriateness and identifying the factors that influence the outcomes (*e.g.*, the quality of the therapeutic relationship). The fact remains, however, that there is a paucity of data supporting the efficacy or effectiveness of psychological treatments aimed at improving the mental health of people with ID. Empirical evidence in this area is still substantially limited[55-57] and the number of available studies are insufficient to make conclusive recommendations, although some interventions show promise, they still require testing in larger, more rigorous trials[58].

An example illustrating this dearth of evidence is a February 2021 Web of Science search for publications with "empirically supported" in the title; the search yielded 422 results, with only three including people with ID. The three articles were about the treatment of problem behavior (functional communication as a well-established treatment), phobic avoidance, and pica (behavioral intervention as a well-established treatment).

To begin to address this gap, Gómez and Navas[59] have listed some of the psychological interventions with the most empirical support for the treatment of problem behaviors or psychiatric disorders in people with ID, establishing their degree of recommendation and current level of evidence. Given the breadth of psychological treatments that could potentially be applied to the full range of problem behaviors and

psychiatric disorders in people with ID, in this paper we will use the classification based on the three generations or waves of therapies, described by Pérez-Álvarez[60]. A summary is presented in Table 1.

First-generation therapies

The first generation of behavioral therapy emerged as a rebellion against the prevailing clinical psychology based on psychoanalysis[60], for which the empirical evidence in people with ID was reduced to descriptive or anecdotal data that often generated more pain than progress. In opposition to these psychoanalytic approaches, the paradigms of classical and operant conditioning were advanced[60]. It was this second paradigm that eventually gave rise to behavioral therapy and applied behavior analysis (ABA), which are among the most widely used interventions and for which there exists the most empirical support for its effectiveness in the field of ID[54].

As Hartley *et al*[57] pointed out, interventions based on the principles of functional behavior analysis are, to date, the only ones included in published lists of effective treatments for people with ID. According to Hartley and colleagues, there is also consensus that differential reinforcement of other behaviors and differential reinforcement of incompatible behaviors increase the effectiveness of the intervention when combined with other behavioral techniques. In a review by Campbell *et al*[54] on the evidence-base for effective psychological interventions treating problem behavior in people with ID, functional analysis is categorized at the highest level of evidence (*i.e.*, "A" with at least one meta-analysis, systematic review, or randomized control trial of high quality and consistency) in two of the reviewed studies. For more information about this system of classification, see Campbell *et al*[54].

Functional analysis is a process aimed at understanding and empirically testing the function of a problem behavior and how it relates to events in the individual's environment (antecedents and consequences). Before determining the existence of a behavioral problem, a multidimensional assessment is needed to exclude health or psychological problems, or medication side effects that could account for the observed behavior in the individual. When these possible causes have been ruled out or treated, a functional analysis is carried out to understand the relationship between the problem behavior and its antecedents and consequences. We must not forget that problem behaviors can be an attempt to communicate a need (*e.g.*, pain relief) or desire (*e.g.*, food) by people who may lack the ability to effectively express themselves in other ways.

In this context, the principles of PBS emanate from the field of disability. PBS is based on respect for the person's values, and its effectiveness is evaluated in terms of improvements to quality of life. In fact, person-centered interventions such as PBS are recommended by the National Institute for Health and Care Excellence[61]. Lavigna and Willis[62] reviewed 12 studies that used PBS involving a total of 423 subjects. While the results demonstrated the efficacy of this intervention, most investigations were single case studies or used very small non-randomized sample sizes. In the review by Campbell *et al*[54], studies using PBS were graded at a "B" level of evidence (*i.e.*, well-conducted clinical studies but no randomized clinical trials directly applicable to the target population, and demonstrating overall consistency of results) and "C" level (*i.e.*, widely held expert opinion but no available or directly applicable studies of good quality). The exception was the intervention by Hassiotis *et al*[63], a randomized controlled trial in which the combination of ABA-PBS together with a standard intervention was shown to be more effective than the standard treatment alone in reducing problem behaviors of lethargy and hyperactivity. McGill *et al*[64] demonstrated using a cluster randomized controlled trial of setting-wide PBS intervention was effective in significantly reducing problem behaviors in social care settings.

Second-generation therapies

The second generation evolved from the convergence of cognitive and behavioral therapy. Cognitive behavioral therapy (CBT) deconstructed the contextual and idiographic character of behavioral therapy to understand cognitions as the cause of emotional and behavioral problems, associating such cognitive "defects" with specific disorders[60].

Despite a paucity of evidence of its efficacy in people with ID, CBT has generated much interest and is often considered potentially useful, taking into account the significant methodological limitations of published studies. According to the research reviewed in a meta-analysis by Vereenooghe and Langdon[65], CBT could be a potentially effective treatment for anger and depression (with better outcomes in individual over group-based interventions). Roberts and Kwan[66] found that CBT

Table 1 Psychological interventions with empirical support for people with intellectual disability

Generation	Intervention	Goal	Degree of recommendation
First: Behavioral therapies	Applied behavior analysis	Problem behaviors	A
	Positive behavior support		B
Second: Cognitive-behavioral therapies	Cognitive-behavioral therapy	Anger, aggression; Depression	C
Third: Contextual therapies	Mindfulness-based therapy	Aggression	D
	Mindfulness-based positive behavior support	Problem behaviors	
	Compassion-focused therapy	Self-criticism unfavorable social comparison; Negative social comparison	D
	Dialectical behavior therapy	Wellbeing	D
	Acceptance and commitment therapy	Obsessive thoughts	D

significantly reduced anxiety in adults with mild to moderate ID as measured by self, proxy, and clinician reported outcome measures.

While preliminary research exists evaluating the use of CBT for adults with ID, the potential use of CBT among children and adolescents with ID is significantly under researched[67]. To the authors' knowledge, the only specifically adapted CBT program for children with ID is Fearless Me!©[67], a multimodal CBT program combining both face-to-face sessions and an online component. It is designed for children and adolescents with mild to moderate ID with the aim of helping them learn to manage and overcome anxiety.

Since cognitive therapies rely on verbal skills and the person's ability to self-report emotions and feelings, they need to be adapted for use in people with ID. The level of adaptation will depend on the person's level of support needs. The duration of the intervention will be longer and will require a greater number of sessions than for people without ID. National Institute for Health and Care Excellence (NICE) guidelines[68] recommended adapted CBT for the treatment of depression and anxiety disorders in people with ID, while acknowledging that the quality of evidence on its effectiveness in this population is low.

Mindfulness-based cognitive therapy is a form of CBT that merits particular attention, since it requires less dialogue with the therapist for the client to become aware of and normalize their emotions or bodily sensations, without applying unsuccessful efforts to discard those experiences. Abstract notions are simplified and made more concrete for people with ID through a series of adaptations. For example, Idusohan-Moizer *et al*[69] described and implemented a 10-session program to treat depression and anxiety in adults with ID. The intervention used mindfulness in breathing and basic yoga stretches characteristic of this approach, which they combined with metaphors and analogies typical of the third-generation therapies we examine in the next section. Although the results indicate a reduction in symptomatology, they should be interpreted with some caution because of issues in determining the specific contributory variables.

Third-generation therapies

Originating as a protest against cognitivism, the third generation of behavioral therapy evolved from developments in behavior analysis, radical behaviorism, and an interest in Skinner's verbal behavior. As pointed out by Pérez-Álvarez[60], contextual therapies are a response to the dissatisfaction with statistical diagnostic systems (DSM/ICD), by considering transdiagnostic dimensions (*e.g.*, hyperreflexivity) rather than nosological categories, and by advocating therapeutic principles (*e.g.*, activation and acceptance) rather than specific techniques or treatments. Third-generation therapies explain problems (as is the case in the field of disability) in interactive, functional, and contextual terms, not as something that is defective in the brain or person, in society or culture, but in the co-evolutionary interaction of the individual and the context in which he or she develops. Further, the effectiveness of these therapies is measured by personal achievements in different life domains (and not by reducing a list of symptoms); hence they align well with the current understanding of

interventions for people with ID, where success is measured in terms of supports and quality of life[50,70].

Patterson *et al*[71] highlighted several important findings in their recent review of third-generation therapies for adults with ID. First, only one of the 20 studies that met the inclusion criteria was a randomized controlled trial; the others were single case studies or single group designs with pre- and post-test evaluation. In all, 45% of the included studies used mindfulness-based therapy (MBT), 30% dialectical behavior therapy (DBT), 15% compassion-focused therapy (CFT), and 10% acceptance and commitment therapy (ACT). Adaptations included modifying the language, concretizing abstract concepts, chunking information, using physical and visual prompts, providing additional time to process information, checking whether participants understood, using role play and experiential exercises, reducing the duration of sessions, and involving carers. On average, interventions were conducted over a 35-wk period and included eight sessions, with each session lasting between 30 min (individual therapy) to 120 min (group therapy). Third-wave therapies improved some symptoms of psychiatric disorders for some adults with ID, but were highly effective at reducing problem and offending behavior in the community, enabling participants to maintain "at-risk" placements.

Singh *et al*[72] tested the effectiveness of mindfulness-based PBS, a customized form of MBT that enables parents and other caregivers to reduce their reported psychological stress to normative levels through mindfulness procedures and to support children with ID to self-manage their problem behaviors through PBS, reporting significant reductions in aggression and disruptive behavior and increases in compliance behaviors. *Meditation on the Soles of the Feet* is one of the few yet most cited resources to have been specifically developed for the treatment of anger and aggression in people with ID[73]. It involves the person shifting their attention from an emotionally intense situation to an emotionally neutral part of the body, the soles of their feet. Other techniques used are "mindful observation of thoughts" (*i.e.*, focusing on breathing, visualizing, and observing thoughts like clouds passing through the consciousness) and observation of breathing or focusing on noises and objects in the environment. While the duration and form of mindfulness training varies across studies, "soles of the feet" training generally includes intensive weekly or daily sessions of supervised role-playing, practice, and homework. Newer promising mindfulness-based programs in the self-management of aggression are *Surfing the Urge*[72] and *Stop, Observe, Breathe, Expand, and Respond Breathing Space*[74]. Despite the limited and weak evidence, existing studies suggest that mindfulness-based programs are effective when applied individually, in groups, or in the community, as well as when parents or support persons are trained in their use, especially for the treatment of aggressive behavior[75-77]. When working with people with ID, however, it is more advisable to apply the programs individually[78].

DBT, which is aimed primarily at reducing behaviors such as self-harm, also has applications and adaptations in the field of ID. The review conducted by McNair *et al*[79] described seven studies on DBT adaptations for use with individuals with ID, but the quality of evidence of its efficacy was rated as methodologically "weak"; the reasons cited included the small number of participants, the absence of a comparison group, and the lack of specificity regarding the goals of the therapy. Glicksman *et al*[80] proposed using this therapy in conjunction with two core models from the field of ID: the person-centered model and the rights-based model. Hewitt *et al*[81] observed that improvements in scores on measures of psychological well-being, psychological distress, and quality of life appeared to be maintained at 6-mo follow-up, but scores at 2-year follow-up suggested a return to baseline for three participants who attended a DBT group for people with ID. In another investigation, Pearson *et al*[82] interviewed 11 individuals with ID about their experiences with this therapy, and noted that the empowering and validating environment created within DBT appeared to facilitate them having a voice in sessions, as individuals described asserting their needs, exerting control, and showing agency around their learning. They also experienced a positive therapeutic relationship, where the relationship was characterized by trust, validation, attunement, availability, empowerment, and a nonjudgmental stance. Moreover, participants described using skillful behaviors and generalizing these skills to other settings.

CFT is another approach that is gaining traction in the field of ID. The adaptation of this therapy for use in people with ID, proposed by Clapton *et al*[83], consisted of presenting the psychoeducational material in a more concrete and visual manner, avoiding or minimizing the use of abstract language, producing a support manual with simple summaries (written and visual information) for each session's specific purpose, and designing practices and exercises to be done at home (*e.g.*, use of colored

sand and water in a bottle to demonstrate the purpose of calming mind and body). The program, consisting of six sessions of approximately 90 min each, was rated as safe, accessible, and useful by the individuals with ID. The main difficulty with this intervention reported by participants was similar to what tends to be reported by participants from the general population: the initial challenge of being able to receive and generate compassion for oneself. The evidence of the efficacy of CFT, however, is based only on this one study with a pre-post evaluation of six people (in which a significant decrease in the level of self-criticism and unfavorable social comparison was observed); and another by Goad and Parker[84] involving two groups of five and six people (in which clinically — but not statistically — significant differences were found).

Fewer studies have been published on treating this population with ACT, a behavioral-contextual approach that combines behavioral change techniques, present moment awareness, and acceptance procedures. A recent review by Byrne and O´Mahony[85], that included eight studies that used ACT with individuals with ID and/or ASD, concluded that ACT may be a useful intervention in reducing psychological difficulties and improving adaptive functioning. However, the small number of individuals included in the sample, as well as the poor methodological rigor of these studies, limit conclusive generalization of these findings. Brown and Hooper[86] outlined how the ACT model was adapted to treat Sarah, 18 years old, who had moderate/severe support needs and was experiencing depressive and anxious thoughts. Similarly, Pankey and Hayes[87] applied a four-session ACT intervention with a young woman with ID (intermittent support needs) and psychosis, and obtained limited but encouraging results.

In sum, it should be reiterated that all of these studies on the use of third-generation therapies in people with ID are quite preliminary and have major limitations (small sample sizes, absence of a control or comparison groups, insufficient evidence of the validity of the assessment instruments used); at best, we can conclude that these treatments show promise, but more effectiveness research is needed.

CONCLUSION

The significant conceptual changes that are taking place in the field of ID have important implications for the work of health professionals and their role in diagnosis, classification, and supports planning. For appropriate and accurate decisions to be made, Schalock *et al*[6,88] recommended: (1) Ensuring that the required criteria for a diagnosis of ID are met; (2) Understanding related constructs and using precise terminology; (3) Recognizing the different conceptions of disability and perspectives that explain ID; (4) Using evidence-based practices in the design and provision of systems of supports[89]; and (5) Approaching subgroup classification as a post-diagnostic strategy, with a specific purpose and based on an explicit classification framework (*e.g.*, according to support needs).

It is also important to bear in mind that, despite the occurrence of diagnostic overshadowing, people with ID have not escaped the omnipresent power of the marketing of psychotropic medications. The medicalization of the lives of people with ID has been promoted at the expense of psychotherapies that, although requiring more effort, have proven efficacy in people without disabilities. We must, therefore, exercise extreme caution to avoid pathologizing people's everyday lives.

In terms of empirically supported psychological treatments, there is an urgent need to improve preventive measures and facilitate access to appropriate, efficacious, and ethical psychological treatments for people with disabilities. To this end, additional and more robust research in this area should be considered a priority, especially in light of the remarkable paucity of reliable empirical evidence for this population. The failure to meet the needs of people with ID and problem behaviors or psychiatric disorders is a clear violation of their rights[49].

Without wishing to undermine the positive examples of second-generation CBTs being adapted for use with people with ID, we believe it would be contradictory to recommend their use given the need to move away from deficit-based models in order to understand ID. Because of their contextual approach, in contrast to the medical model, first- and third-generation therapies are, in our view, more suitable. For third-wave therapies in particular, there is an urgent need for research into outcome measures with evidence of validity in homogeneous and adequately sized study groups; as well as evidence of cost and efficacy. In this regard, the evaluation of personal outcomes related to quality of life is highly recommended as a way of testing

the efficacy of psychological treatments[90].

In accordance with the NICE guidelines[68], psychological interventions should be tailored to the preferences of people with ID, their level of understanding, their preferred mode of communication, their strengths, needs, and other associated conditions. In addition, interventions should respect the individual's privacy (although they should also seek the collaboration of family and primary support providers) and provide additional supports during and between sessions. To achieve this aim, it is not enough for health care professionals — particularly psychologists and psychiatrists — to know what is ID. They must also learn about the relevant ethical aspects, principles, and values, including supports, inclusion, rights, self-determination, and quality of life[50]; and be willing to coordinate with professionals from other social, education, and health services.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 1053-1064

DOI: 10.5498/wjp.v11.i11.1053

ISSN 2220-3206 (online)

MINIREVIEWS

Phantom bite syndrome: Revelation from clinically focused review

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Author contributions: Tu TTH, Watanabe M, Umezaki Y and Toyofuku A were involved in manuscript drafting; Nayanar GK, Motomura H and Sato Y critically revised the manuscript; All authors read and approved the manuscript.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Supported by JSPS KAKENHI Grant, No. 19K10328 (to Professor Toyofuku A).

Country/Territory of origin: Japan

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

Phantom bite syndrome (PBS), also called occlusal dysesthesia, is characterized by persistent non-verifiable occlusal discrepancies. Such erroneous and unshakable belief of a "wrong bite" might impel patients to visit multiple dental clinics to meet their requirements to their satisfaction. Subsequently, it takes a toll on their quality of life causing, career disruption, financial loss and suicidal thoughts. In general, patients with PBS are quite rare but distinguishable if ever encountered. Since Marbach reported the first two cases in 1976, there have been dozens of published cases regarding this phenomenon, but only a few original studies were conducted. Despite the lack of official classification and guidelines, many authors agreed on the existence of a PBS "consistent pattern" that clinicians should be made aware. Nevertheless, the treatment approach has been solely based on incomplete knowledge of etiology, in which none of the proposed theories are fully explained in all the available cases. In this review, we have discussed the critical role of enhancing dental professionals' awareness of this phenomenon and suggested a comprehensive approach for PBS, provided by a multidisciplinary team of dentists, psychiatrists and exclusive psychotherapists.

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Received: May 7, 2021
Peer-review started: May 7, 2021
First decision: June 5, 2021
Revised: June 10, 2021
Accepted: August 30, 2021
Article in press: August 30, 2021
Published online: November 19, 2021

P-Reviewer: Avtaar Singh SS
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Guo X

Key Words: Phantom bite syndrome; Occlusal dysesthesia; Clinical manifestation; Pathophysiology; Treatment strategy; Psychopharmacology

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Core Tip: Generally, in dentistry, uncomfortable occlusal sensations are a common finding among patients while phantom bite syndrome (which is distinguishable if ever encountered) is quite rare. These patients present with non-verifiable occlusal discrepancies with strict demands for bite correction and remarkable psychological distress. This might lead to serious consequences on patients' life quality, relationship with family, financial loss, career disruption or even suicidal thoughts. Recent studies have revealed unexplained diversity patterns among phantom bite syndrome's clinical manifestation and functional brain imaging, which likely represent the available subphenotypes of this syndrome. Further research must be focused on elucidating pathophysiological mechanisms to pave the way for efficient treatment strategy.

Citation: Tu TTH, Watanabe M, Nayanar GK, Umezaki Y, Motomura H, Sato Y, Toyofuku A. Phantom bite syndrome: Revelation from clinically focused review. *World J Psychiatr* 2021; 11(11): 1053-1064
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1053.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1053

INTRODUCTION

A general dentist might come across many patients with disturbing or uncomfortable bite sensations in their daily practice. Most of the time, these typical complaints are due to reasons such as new crown delivery, dental restorations, orthodontic treatment and temporal mandibular joint dysfunction. Subsequently, dentists will perform some occlusal adjustments or provide a specific therapy, if on examination they observed any abnormal intercuspation or contact patterns. However, apart from these ordinary cases, there are some cases where patients present with non-verifiable occlusal discrepancies with strict demands for bite correction.

This phenomenon, named "phantom bite syndrome" (PBS), was firstly described by Marbach in 1976 with a report of two female cases[1,2]. The term was originally inspired by phantom limb pain, because it was suggested that what occurred after dental treatment in patients with hypochondriacal or severe personality disorder resembles the "ego defense" or "denial of loss" mechanism in postamputation patients [2]. Earlier, Posselt had mentioned this unusual sensation as a hyperawareness named "positive occlusal sense" in his textbook from 1960, saying "after occlusal grinding or adjustment, some person with a nervous predisposition may become too conscious of their own occlusion"[3]. However, Marbach's evocative illustrations are useful for clinicians to visualize better the phenomenon.

In 1997, Clark *et al*[4] proposed an alternative term: "Occlusal dysesthesia". Nowadays, this is commonly used to define "a persistent (more than 6 mo) uncomfortable bite sensation, which does not correspond to any physical alteration related to occlusion, pulp, periodontium, muscle or temporomandibular joint and cause significant functional impairment"[5]. Since then, there have been dozens of published cases regarding this phenomenon, but few original studies have been conducted. From the compiled case reports, it was observed that PBS patients were never satisfied with occlusal treatment resulting in "dental shopping", and they refused to see psychiatrists because of their belief in "ideal bite correction" (Figure 1). Besides, neither an official classification nor any widely accepted treatment protocol currently exists. Given the new shreds of evidence from recent research, we set out to discuss: (1) Demographic characteristics and the typical manifestations of PBS; (2) The debate on etiopathogenesis; and (3) Recommended management strategies.

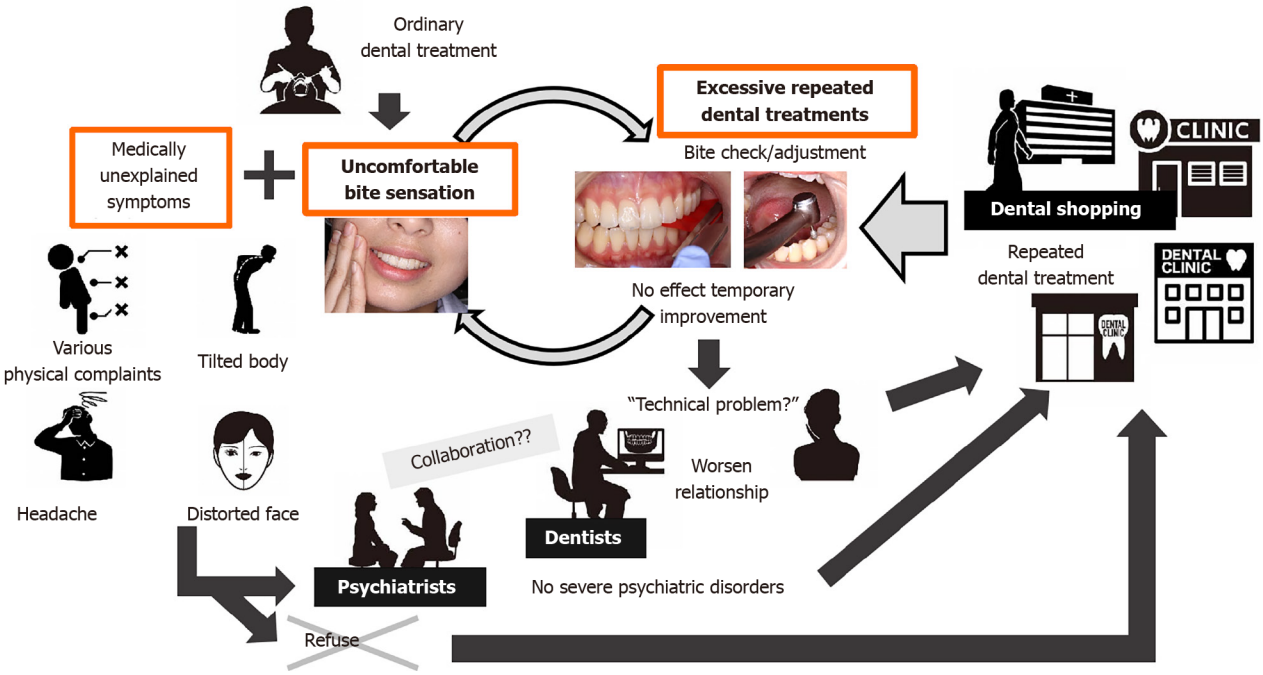


Figure 1 A typical course of phantom bite syndrome. Those nomadic patients usually travel from one dentist to another, desperately seeking an "ideal bite correction". They normally refuse to see psychiatrists if being referred.

DEMOGRAPHIC AND THE TYPICAL MANIFESTATIONS OF PBS

Epidemiology

Generally in dentistry, uncomfortable occlusal sensations are a common finding among patients, while PBS (which is distinguishable if ever encountered) is quite rare. According to an email survey sent to United States orthodontists, 75% of respondents recalled encountering at least one patient with typical symptoms of phantom bite during their career, even though almost half of them were unfamiliar with the term itself[6]. Gerstner *et al*[7] in their study found that 20.5% of 127 temporal mandibular disorder (TMD) clinic patients had their uncomfortable bite all the time. However, whether their "discomfort" met the PBS diagnosis criteria was not discussed. In a study by Watanabe *et al*[8], PBS only accounts for less than 10% of outpatients who visit a specialized clinic of oral psychosomatic disorders. The discrepancy of the ratio between cases encountered by United States orthodontists and the cases in specialized clinic might be attributed to their obsession for "ideal bite correction" as mentioned above. Yet, to our knowledge, there has been no study that estimates the incidence of this phenomenon in the general population.

Demographic characteristics

Back in 2012, there were no original PBS data published. Hara *et al*[9] were the first to combine the results from 37 case reports in their first systemic review. Later, in two retrospective studies done by two different Japanese teams, the data confirmed similar patterns of female predominance, mean age and symptom duration. In particular, the female ratio varies from 72% to 84%, while the mean age at the initial visit ranges from 51.7 years to 53.1 years[8,10]. In terms of symptom duration, 39.5% of patients suffered from an abnormal bite for more than 5 years[8]. Except for the 2 cases that started since adolescence (as both described by Marbach), the majority developed their onset symptom around the age of 45[2,9].

One frequent observation among many PBS cases is that the first mild discomfort is often associated with some certain dental treatment (*e.g.*, restorations, orthodontic treatment), then it becomes worse after further occlusal adjustment or extensive dental interventions (*e.g.*, replacing crowns, extraction)[2,8,11-17]. However, 26.2% of 130 PBS patients reported symptoms that developed spontaneously or with triggers other than dental therapy. Looking for an ideal bite correction, they then visited approximately 4.4 ± 3.4 dental clinics[8]. The highest record belongs to one male patient who attended at least 200 appointments with 20 different dentists in 6 years[11]. To be able to pursue such a frustrating, time and money-consuming journey, the PBS patients are normally

assumed to be of moderate to high socioeconomic status[11,15,18]. Such impression comes from expert consensus, but in fact, the situation may vary depending on national medical systems and policy.

Comorbid psychiatric disorders

In the very first announced case, Marbach suspected that PBS patients were mentally ill with delusion and paranoia, saying "hope for these unfortunate patients lies in part in the ability to make psychiatric research available for dentists"[2]. This argument was questioned later by Greene and Gelb, when 4 out of 5 patients in their report did not qualify for any diagnosis of mental disorders[19]. From a Japanese prosthodontist's report, 46.2% of the patients complaining of occlusal disharmony had neuroticism, and 53.8% had manifest anxiety[20]. This aligned with recent reports whose prevalence of psychiatric comorbidity (depression, anxiety disorder, insomnia, somatic symptom disorders) was between 45.9% and 59.51%. Schizophrenia and severe personality disorders were rare[8,10]. Since PBS patients mainly complain of occlusal discomfort and rarely present severe psychiatric comorbidities, they seldom are provided active psychiatric treatment.

Typical manifestations of PBS

Despite the lack of official classification and guidelines, many authors agreed on the existence of a PBS "consistent pattern" that clinicians could easily recognize and should be made aware[9,18,21,22]. A list of frequently observed clinical manifestations is summarized in Table 1.

Firstly, the occlusion or bite would be the center of their complaints, even though they may be expressed in many different ways (see Table 2). This would make PBS distinguishable from other oral conditions characterized by abnormal sensations or idiopathic pain without evident causes such as burning mouth syndrome, oral cenestopathy and atypical odontalgia. Besides, PBS could be observed together with TMD and is sometimes even categorized as TMD's subgroup[5,23-25].

Another important clinical aspect rarely mentioned in the literature is patients' emphasis that their occlusal problems lead to concomitant somatic symptoms in other body parts (*e.g.*, idiopathic headache, musculoskeletal pain)[8,11,12,16,22,26]. "Our teeth is not separated from the body, after all", one patient even said[2]. Therefore, they firmly believe that all of their somatic dysfunctions would be cured if and only if their bites are corrected (Figure 2).

There has been no official record of specific triggers other than dental interventions at symptom onset. However, some cases reported patients who experienced a traumatic accident or underwent a pressured period of life (*e.g.*, divorce, change of jobs), with or without dental treatments[8,12]. Lack of a dental trigger becomes a predictor for psychiatric comorbidity, which affects the treatment outcome[8].

When patients describe their symptoms, they tend to use dental professional terminologies, even when they only have superficial knowledge about their conditions [2,11,13]. Not only equipping themselves with a lot of arguments and self-research information, they often bring to the appointment pieces of evidence to prove occlusal discrepancies, including their collection of diagnostic casts, occlusal splints, teeth pictures, radiographs or even extremely detailed resume and records from previously failed treatments[2,6,11,18,26,27]. They would, sometimes, describe clearly and confidently that prior incompetent dentists are responsible for their exacerbated symptoms[2,6,11,13,15,28].

From our clinical observation, some patients are more obsessed with the idea of getting their occlusal equilibrium done than the "wrong bite" itself. In many cases, PBS patients even rigorously direct the dentists on what to be done. If not granted desired treatments, these patients would reject any other suggested treatment and quickly drop out after the first or second visit. Once the dentists recognize this pattern, inform patients about their normal examination results and gently recommend another specialist/psychiatric assessment, this rational approach will be met with prolonged discussions and denial. Meanwhile, even if patients' demands are met, the absence of any tangible result will reinforce the existing erroneous belief that the occlusion problem has not been properly addressed. Dental services often affect PBS patients iatrogenically for worse (Figure 3). Such a vicious cycle of dental shopping thus continues.

In terms of psychological impacts, a study by Tsukiyama *et al*[29] showed significantly higher scores of somatic symptoms and depression subscales in PBS patients in comparison with those of control groups. Nevertheless, as the author self-declared, these differences "only indicate that the patients may have psychiatric problems, not possible to prove that they have mental disorders". Even in PBS cases

Table 1 Clinical characteristics of phantom bite syndrome

	Clinical characteristics
1	Preoccupation with their dental occlusion and an enormous belief that their dental occlusion was abnormal
2	A long history of repeated dental surgery treatment failures with persistent requests for the occlusal treatment that they are convinced they need
3	A relatively high intelligence and socioeconomic status enabled them to undergo endless costly and time consuming dental treatments
4	Despite repeated failures of dental surgery, persist in seeking bite correction from a succession of dentists
5	A strong resistance to referral to psychiatrists and stick to dental procedures
6	A favorable attitude to dentists at first, gradually blaming them for the exacerbated symptoms, finally dropping out with disappointment
7	A tendency to use dental jargon
8	Bringing to the appointment pieces of evidence to prove occlusal discrepancies (radiographs, study cast, temporary crowns, mouthpieces, *etc.*)

Table 2 Summary of frequent complaints observed in patients with phantom bite syndrome and proposed terminologies

Terminologies
Phantom bite syndrome
Occlusal dysesthesia
Occlusal hyperawareness
Occlusal hypervigilance
Occlusal neurosis
Positive occlusal sense
Persistent uncomfortable occlusion
Frequent complaints
Abnormal/uncomfortable bite
My bite is off/too high
My jaws are not biting correctly
Jaw looseness and weak bite
Uneven dental bite
Feel uneasy with the bite
I try maneuver to position the bite correctly
I don't know where my teeth belong anymore
Lack of familiarity with my own bite

without psychiatric comorbidity, psychological distress is remarkable. They might lead to serious consequences on patients' life quality, relationship with family, financial loss, career disruption or even suicidal thoughts[2,11,12,15]. Corresponding dentists, if trapped in these unusual cases, will quickly find these patients oppose any treatment and become increasingly challenging to manage. The worst scenarios would be litigation problems between patients and dentists[2,11,13].

THE DEBATE ON ETIOPATHOGENESIS

Initially, PBS was viewed as a psychotic disorder that was "rarely brought to the attention of psychiatrists" before being classified into monosymptomatic hypochondriacal psychosis (MHP)[2,18]. This speculation arises from the similarity between "wrong bite" obsession in PBS patients and "an erroneous and unshakable belief in a distorted body image" in MHP phenomenon[18]. In other words, PBS was suggested to be a sub-phenotype of MHP present in dental clinics, comparable with parasitosis that is often seen by dermatologists, sharing the common features of equal gender

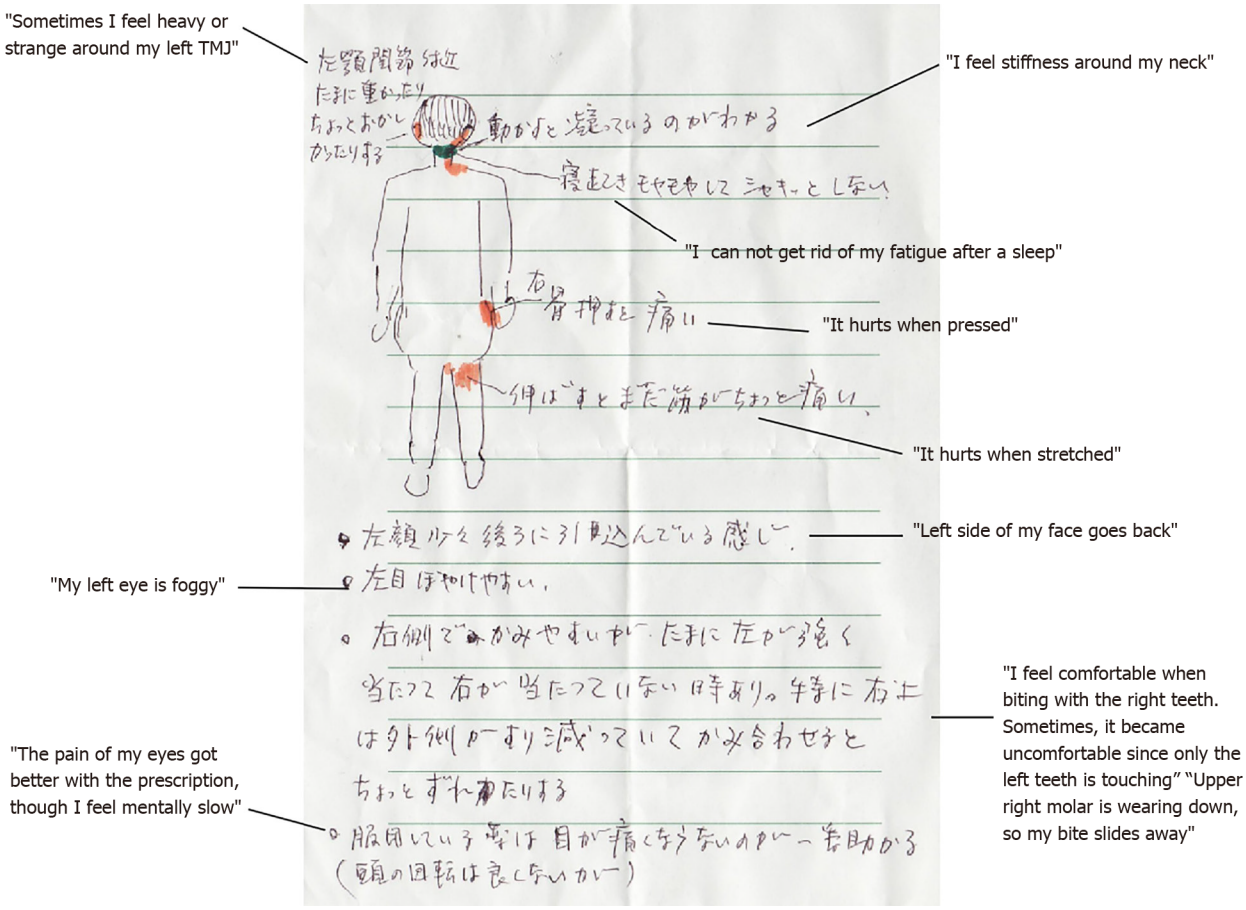


Figure 2 A written self-report of patient's multiple comorbidities of medically unexplained symptoms (*e.g.*, headache, dizziness, neck and back pain, ambulatory impairment, numbness of hands and legs) associated with occlusal symptoms.



Figure 3 Occlusal view of mandibular arch in a 60-yr-old female phantom bite syndrome patient. Clinical examination revealed unnatural restorations for dentition owing to the fullest effort of dentists.

distribution and early adulthood onset. Unfortunately, this observation seems no longer to concur with recent demographic reports[8-10].

Twenty years later, this "psychodynamically oriented view" is replaced by the same author[30]. At this time, Marbach[30] adapted Melzack's theory of neuromatrix and re-discussed PBS's pathophysiology in a shared context with phantom tooth pain/atypical odontalgia[30,31]. The key element of this theory is that there exist individual differences in self-knowledge of occlusion, namely occlusal neurosignature.

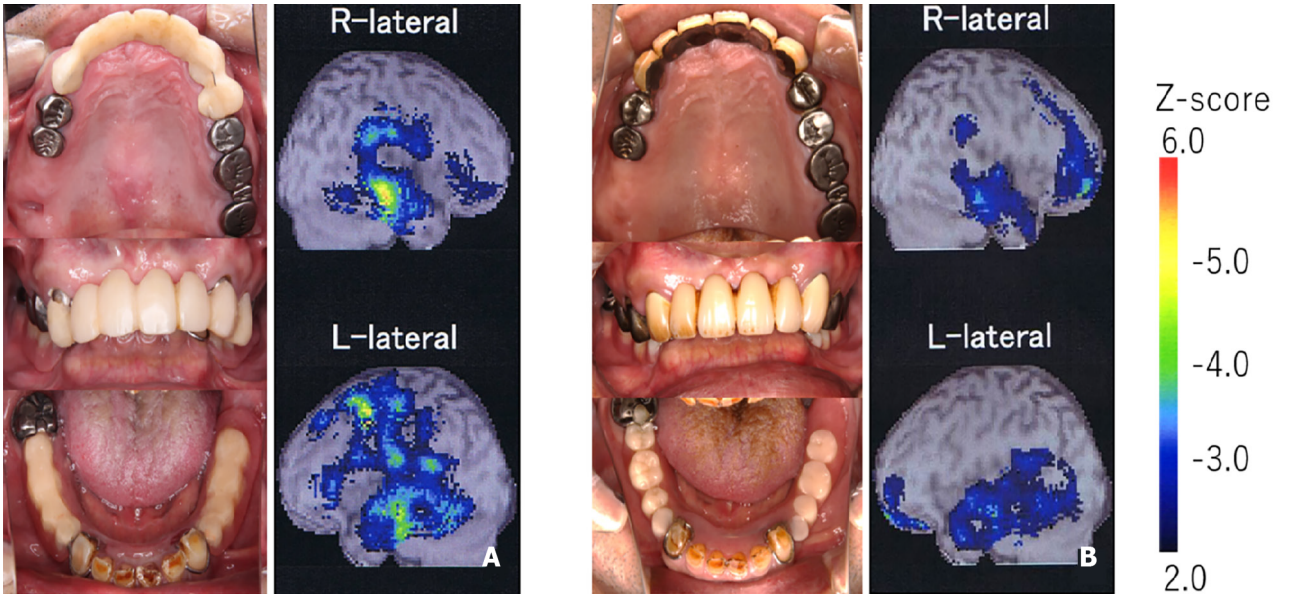


Figure 4 Intra-oral photography and regional cerebral blood flow increasing map before and after phantom bite syndrome psychopharmacotherapy. The color bar indicates the Z-score comparing normal controls. A and B: The before (A) and after (B) pharmacotherapy. As the phantom bite symptom decreased, the asymmetrical regional cerebral blood flow pattern attenuated, and dental treatment was finally completed. Citation: Umezaki Y, Watanabe M, Takenoshita M, Yoshikawa T, Sakuma T, Sako E, Katagiri A, Sato Y, Toyofuku A. A case of phantom bite syndrome ameliorated with the attenuation of the asymmetrical pattern of regional cerebral blood flow. Jpn J Psychosom Dent 2013; 28: 30-34. Copyright ©The Japanese Society of Psychosomatic Dentistry 2013. Published by The Japanese Society of Psychosomatic Dentistry[16].

Such a unique coherent unit in the brain was created and is influenced by lifetime intercuspation and other tooth contacts. Whenever a dental intervention or routine adjustment is made, it would send a new input to the central nervous system. In the case of PBS patients, it is difficult for their neuromatrix to adapt to even a minor change, and they thus soon become unable to recognize the original bite itself[30].

From 1993 to 2000, Toyofuku[32] conducted a clinical study using psychosomatic approaches to treat 16 serious PBS cases during hospitalization. As a result, it was observed that 15 of 16 PBS patients responded to the combination therapy of tricyclic antidepressants and supportive psychotherapies. From the result of these clinical observations, the author hypothesized that PBS might be due to several biochemical disorders involving neurotransmitters in the brain, the wrong connection between occlusion and medically unexplained complaints due to cognitive processes in the higher centers of the brain. This working hypothesis, however, had not been recognized widely due to the language barrier of Japanese publications. Notably, in the follow-up study 5 years later, about one-third of these cases began to complain of request for needless dental treatments again. Besides, a review of 130 PBS patients suggested that PBS is seldom associated with psychotic disorders. Central neuromodulator (antidepressant or antipsychotic) therapy may be effective for PBS. Most of these medications were given at very low "non-psychiatric" doses"[33]. These findings support the working hypothesis, suggesting the role of biochemical disorders involving neurotransmitters in the brain of PBS patients.

In 2003, Clark and Simmon[5] proposed the theory of altered oral kinesthetic ability as another possible mechanism of PBS. In their speculation, some dysfunctions of muscle spindles in the jaw closers muscles would be responsible for the impairment of an individuals' ability in mandibular position discrimination. They did not invalidate Marbach's theory of diagnosable psychiatric disorders but rather agreed with Green and Gelb[19], stating that although patients' symptom and behaviors have certain psychological impact, the main underlying cause would be the unknown alterations in proprioceptive input transmission. Contrary to their expectation, the next two experimental studies comparing sensory perceptive and interdental thickness discriminative capacities in PBS and the control group both revealed insignificant results[29,34]. Nevertheless, the possibility that the sensory test was not sensitive and accurate enough to tell the threshold differences could not be excluded.

Given this unsettled controversy, "brain imaging techniques…can be utilized to evaluate whether cortical map representations in fact correspond to patient's subjective occlusal complaints…", Hara *et al*[9] suggested in their review. In 2013,

Umezaki *et al*[16] conducted a single-photon emission computed tomography in a PBS patient, revealing asymmetrical cerebral blood flow (CBF) patterns in the frontal lobe region. Interestingly, 1 year after taking psychopharmacology, not only had the patient's symptoms remarkably improved, but the asymmetry patterns also attenuated. This finding reinforced the "altered central processing" theory, suggesting the involvement of central nervous system dysfunction in PBS manifestation. However, in a later case-control study conducted by the same research group, regional CBF (rCBF) in 44 PBS patients and 12 control subjects had insignificant differences. The author admitted that the initial idea of comparing one whole group of PBS with normal controls was "inappropriate" and interpreted this negative results as a reflection of the heterogeneous nature in PBS. A secondary analysis of these data later revealed different rCBF patterns are in accordance with certain clinical patterns, such as laterality of the symptoms or behavior of blaming dentists. In particular, PBS patients with right-side symptoms have significant right-side predominant parietal asymmetry and left-side predominant thalamus asymmetry[28]. Disturbance in the parietal area, which includes the secondary sensory cortex, and thalamus that relay information between different subcortical areas and the cerebral cortex, might imply the complexity of PBS symptoms. In the study, the tendency of frontal lobe asymmetry is also reported as the same with experimentally reproduced occlusal discomfort.

Generally speaking, all of these above interpretations were substantially built upon personal judgment and limited clinical observations. So far, none of these proposed theories fully explain all the available cases. For example, there are PBS cases (where patients had neither psychiatric disorder nor abnormal psychological condition) that cannot be explained using the theory of psychopathological influences alone[8,10]. Besides, there are also PBS patients whose symptoms spontaneously developed, meaning there are no dental treatments related inputs to trigger peripheral alterations. As long as this controversy remains unsolved, neither specific diagnostic testing nor effective treatment can be sufficiently developed.

RECOMMENDED MANAGEMENT STRATEGIES

Based on these perspectives of etiology and pathogenesis, various authors proposed different strategies. However, they all agree that treatment should primarily focus on patients' education and therapies that improve overall function and well-being[9,23,27,35]. In this review, apart from those treatments, we want to discuss further other underestimated perspectives; including professional education, psychopharmacotherapy, successful guidance and reliable therapeutic relation.

Professional education

First and foremost, dental treatment would not be helpful and should be avoided. As many authors stated, PBS patients are considered to be "refractory to any dental treatment"[2,6,9,11,14,18,22]. However, they will always look for help from dentists, whom they believed to be the only people with enough expertise to understand their complaints and then be able to provide a "full bite correction". In fact, on oral examination, some occlusal discrepancies may be detected, but they were far from the root cause of patients' suffering[5,22]. Besides, a normally good occlusion can always be enhanced to become an ideal one with dentists' intervention[23]. Such conventional treatment might initially relieve symptoms, but sooner or later, the condition only becomes worst since the patients' occlusion was more and more distorted from the original. Hence, to prevent inappropriate, time-consuming, irreversible, extensive treatments; enhancing dental professionals' awareness of this phenomenon is critical. Clinicians should be aware that there is no strong evidence to support that theoretically ideal occlusion must be fulfilled for a successful outcome of prosthodontic treatment[36].

Interestingly, we observed that the majority of PBS original research, including retrospective and case-control studies, came from either Japanese or German research teams[8,10,16,21,29,34,37]. This suggests that there are licensed specialists who treat the syndrome at specialized clinics in these two countries. In particular, thanks to the inclusion of PBS and other phenomena of oral psychosomatic disorders in the undergraduate dental curriculum of some Japanese universities since the early 2000s, a general dentist will be able to notice an early case of PBS and refer them to relevant treatment centers.

Table 3 Summary of medications used in phantom bite syndrome's management

Classification	Drug's name	Period of follow-up	Side effects	Treatment outcome	Mechanism	Level of evidences	Ref.
D2 blocker	PimozideHaloperidol	No report	No report	No report	Prescribed as a treatment for monosymptomatic hypochondriacal psychosis	Expert's opinion	Marbach [2], 1978
D2 partial agonist	Aripiprazole	Average 59 d from initial administration to clinical improved day	Drowsiness, constipation, weight gain, nausea, diarrhea, staggering, dizziness, malaise, irritation, headache	37% improved; 40.7% no change, 22.3% discontinued	Unspecified	Retrospective study, *n* = 27	Watanabe *et al*[8], 2015
Anticonvulsant	Clonazepam	No report	No report	No report	Reduce anxiety and increase tolerance to the symptom	Expert's opinion	Clark *et al* [23], 2005
Tricyclic antidepressant (TCA)	Dothiepin	Unspecified	Unspecified	Generally recovered	Prescribed as a treatment for somatic symptom disorder	Single case report	Wong and Tsang[12], 1991
	Amitriptyline	390 d	No	Significant improvement	Unspecified	Single case report	Umezaki *et al*[16], 2013
		Average 75 d from initial administration to clinical improved day	Drowsiness, constipation, weight gain, nausea, dry mouth, malaise	44.8% improved; 41.3% no change, 13.9% discontinued	Unspecified	Retrospective study, *n* = 29	Watanabe *et al*[8], 2015
	Paroxetine	No report	Drowsiness	1/3 improved; 2/3 no change	Unspecified	Retrospective study, *n* = 3	Watanabe *et al*[8], 2015
Serotonin-norepinephrine reuptake inhibitor		Average 152 d from initial administration to clinical improved day	Drowsiness, constipation, nausea, dysuria, pollakiuria, staggering, dizziness, malaise	4/7 improved; 3/7 no change	Unspecified	Retrospective study, *n* = 7	Watanabe *et al*[8], 2015
	Duloxetine	Average 28 d from initial administration to clinical improved day	Drowsiness, constipation, nausea, decreased appetite	3/7 improved; 4/7 no change	Unspecified	Retrospective study, *n* = 7	Watanabe *et al*[8], 2015
		5 mo	No report	Symptom improved	No report	Single case report	Bhatia *et al* [39], 2013
	Escitalopram	Average 18 d from initial administration to clinical improved day	Drowsiness, staggering, dizziness, malaise	3/4 improved; 1/4 discontinued	Unspecified	Retrospective study, *n* = 4	Watanabe *et al*[8], 2015
Selective serotonin reuptake inhibitor	Sertraline	Average 79 d from initial administration to clinical improved day	Drowsiness, constipation, nausea, edema, dry mouth, decreased appetite	7/9 improved; 2/9 no change	Unspecified	Retrospective study, *n* = 7	Watanabe *et al*[8], 2015
	Fluvoxamine	Average 24 d from initial administration to clinical improved day	Drowsiness	2/4 improved; 2/4 no change	Unspecified	Retrospective study, *n* = 4	Watanabe *et al*[8], 2015
Noradrenergic and specific serotonergic antidepressant	Mirtazapine	Average 59 d from initial administration to clinical improved day	Drowsiness, constipation, weight gain, nausea, staggering	42.9% improved; 47.6% no change, 9.5% discontinued	Unspecified	Retrospective study, *n* = 21	Watanabe *et al*[8], 2015
Combination of TCA and D2 partial agonist	Amitriptyline; Aripiprazole	41 mo	Staggering	Remarkable improve	Altered biochemical abnormalities related to neurotransmitter and higher brain	Single case report	Umezaki *et al*[16], 2013

					connectivity dysfunction, especially dopaminergic system		
Combination of TCA, benzodiazepine and D2 blocker	Amitriptyline; Lorazepam; Sulpiride	Average 99.8 d for hospitalization and 3.8 yr from discharge	Weight gain, Liver dysfunction, hyperprolactinaemia	15/16 improved	Altered biochemical abnormalities related to neurotransmitter	Retrospective study of inpatients, n = 16	Toyofuku [32], 2000
Combination of D2 blocker and benzodiazepine	Sulpiride; Flunitrazepam	10 mo	No report	Symptom improved	Unspecified	Single case report	Nakamura [40], 1996

Psychopharmacotherapy

In terms of pharmacotherapeutics, although it has never been considered the primary choice of treatment in PBS management, medications appear to be the most applied treatment among clinical studies[8,10,13,18,38-40]. As presented in Table 3, the most frequently prescribed medications are antidepressants and antipsychotics. Originally, Marbach[2] prescribed pimozide and haloperidol, and Wong and Tsang[12] prescribe dothiepin, an antidepressant, since they regard their PBS patient as psychiatric disorder. As the etiological discussion matured, considerations for psychopharmacological mechanisms have been deepened. Other authors also applied psychotropic drugs and suggested such effects were related to biochemical alteration in central nervous system (especially the dopaminergic system)[8,16]. Besides, Clark *et al*[23] recommended clonazepam, an anticonvulsant, mainly for mood stabilizing, anxiety control and patients' distraction. Since results were limited to single case reports, case series and a retrospective analysis study, prospective follow-up or clinical control study will be needed for further verification. At the same time, elucidation of psychotherapeutic mechanism for PBS should be required to be applied at scale.

Successful guidance and reliable therapeutic relation

The assessment of psychological components and the use of appropriate consultants if needed have been recommended[6,9,18,21]. Because dental professionals are not trained to practice psychological evaluation (either distraction or cognitive behavioral therapy), they are advised to refer patients to psychiatric care. However, based on our clinical observation and literature review, this is not always a practical choice. Among 12 cases of PBS in a series collected by Kelleher[11], none was successfully referred to psychiatrists for psychological assessment. Responses included "immediate rejections", "declined help" or "eventually accepted but be extremely bitterly about"[11]. Such reluctance was also observed by other clinicians, saying "many patients will never accept just a referral"[8,13,18]. Ideally, collaborated management provided by dentists, psychiatrists and exclusive psychotherapists would be the best approach. Unfortunately, this is hardly available in the current dental clinic setting.

In addition, the most common barrier preventing a clinician to apply psychopharmacotherapy is persuading patients to accept treatment. According to Watanabe *et al* [8], PBS patients had remarkably high ratios of refusal of pharmacological treatment, especially in those with dental triggers. PBS patients have such a strong belief that only dental treatment can relieve the symptom, resulting in them refusing any therapy other than dental interventions. Such belief like obsession or dominant idea grows stronger *via* repeated dental interventions and temporary relief. In order to shift that insufficient belief and to stop never-ending dental interventions, there needs a positive patient-doctor relationship built upon trust, empathy and efficient communication [22]. In our clinical observation, such evidence of neuromodulators helping to balance rCBF asymmetry patterns in successfully treated PBS cases would aid in patients' understanding of medication necessity (Figure 4)[16].

Treatment for PBS is indeed difficult in the dental setting but not impossible as reported[27]. Prudent patient education with an etiological explanation based on neuroscience including brain images would help PBS patients to understand their situation and to be convinced for pharmacotherapy instead of repeated dental procedures. Moreover, even in cases of acceptance, side-effects and slow drug response would affect patient's tendency to withdraw quickly. It seems to be more related to resistance to taking medication than to actual adverse effects. Careful contact with patients and delicate dosing are important during the follow-up period[8].

CONCLUSION

PBS is a tremendously difficult and unusual dental phenomenon that is underreported and deserves more attention. Recent studies have revealed unexplained diversity patterns among PBS's clinical manifestation and functional brain imaging that likely represent the available sub-phenotypes of this syndrome. Further research must be focused on elucidating pathophysiological mechanisms to pave the way for efficient treatment strategy.

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World Journal of Psychiatry

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World J Psychiatr 2021 November 19; 11(11): 1065-1074

DOI: 10.5498/wjp.v11.i11.1065

ISSN 2220-3206 (online)

MINIREVIEWS

Breast cancer in schizophrenia could be interleukin-33-mediated

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Author contributions: Borovcanin MM and Vesic K contributed equally to this work; Borovcanin MM presented the idea, structured the manuscript, searched the literature, integrated all parts of the manuscript, and drew two figures; Vesic K searched the literature, provided some new insights, and performed the final revision to the manuscript; and both authors read, additionally discussed and approved the final version of the manuscript.

Conflict-of-interest statement: Borovcanin MM has received research funding from Ministry of Science and Technological Development of the Republic of Serbia (NO. 175069); Faculty of Medical Sciences, University of Kragujevac (NO. JP15-05). Vesic K declared no conflict of interest.

Supported by Ministry of Science and Technological Development of the Republic of Serbia (NO. 175069); Faculty of Medical Sciences, University of Kragujevac (NO. JP15-05).

Country/Territory of origin: Serbia

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer

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Abstract

Recent epidemiological and genetic studies have revealed an interconnection between schizophrenia and breast cancer. The mutual underlying pathophysiological mechanisms may be immunologically driven. A new cluster of molecules called alarmins may be involved in sterile brain inflammation, and we have already reported the potential impact of interleukin-33 (IL-33) on positive symptoms onset and the role of its soluble trans-membranes full length receptor (sST2) on amelioration of negative symptoms in schizophrenia genesis. Furthermore, these molecules have already been shown to be involved in breast cancer etiopathogenesis. In this review article, we aim to describe the IL-33/suppressor of tumorigenicity 2 (ST2) axis as a crossroad in schizophrenia-breast cancer comorbidity. Considering that raloxifene could be tissue-specific and improve cognition and that tamoxifen resistance in breast carcinoma could be improved by strategies targeting IL-33, these selective estrogen receptor modulators could be useful in complementary treatment. These observations could guide further somatic, as well as psychiatric therapeutical protocols by incorporating what is known about immunity in schizophrenia.

Key Words: Interleukin-33; Schizophrenia; Breast cancer; Neurodegeneration

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Core Tip: The frequent occurrence of breast carcinoma in female patients with schizophrenia could indicate a specific immunological perturbation in both diseases. A common denominator could be interleukin-33 (IL-33). In this review article, we aim to describe the IL-33/suppressor of tumorigenicity 2 axis as a crossroad in schizophrenia-breast cancer comorbidity. Considering that raloxifene could be tissue-specific and

reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: May 30, 2021
Peer-review started: May 30, 2021
First decision: July 14, 2021
Revised: July 21, 2021
Accepted: September 22, 2021
Article in press: September 22, 2021
Published online: November 19, 2021

P-Reviewer: Valencia GA
S-Editor: Wang JJ
L-Editor: Webster JR
P-Editor: Guo X

improve cognition and that tamoxifen resistance in breast carcinoma could be improved by strategies targeting IL-33, these selective estrogen receptor modulators could be useful in complementary treatment. These observations could guide further somatic, as well as psychiatric therapeutical protocols by incorporating what is known about immunity in schizophrenia.

Citation: Borovcanin MM, Vesic K. Breast cancer in schizophrenia could be interleukin-33-mediated. *World J Psychiatr* 2021; 11(11): 1065-1074
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1065.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1065

INTRODUCTION

The initial question is whether patients with schizophrenia are resistant or more susceptible to developing breast cancer. Recently, it has been reported that the prevalence rate of schizophrenia of 0.3%-0.7% in the world population remains stable [1]. There is a possibility that some mechanisms underlying the pathogenesis of schizophrenia also have beneficial or even protective properties for the onset of some somatic disorders, while others lead to somatic comorbidity and mortality.

Schizophrenia is a neurodegenerative disease with a complex pathogenesis and pathophysiology. This type of disorder is characterized by a chronic course, exacerbations, and progression leading to neurodegeneration over time. Genetic predisposition, individual and environmental factors, and specific immune responses have a significant impact on disease onset and clinical presentation. Moreover, genome-wide association studies in schizophrenia have revealed similar genetic backgrounds with some immunological properties and genetic overlap with breast carcinoma[2,3].

Scientific advances in the last decade have led to the recognition that interleukin-33 (IL-33) and neuroinflammation play a role in some aspects of neurodegenerative diseases. It is possible that IL-33 has various biological activities at different stages of the disease. It is necessary to consider disease progression with exacerbations and neurodegeneration, and to discuss the impact of IL-33 on somatic disturbances.

The alarmin molecule IL-33 as a marker of innate immunity was first studied in different phases of schizophrenia, but also in breast carcinoma patients[4]. In summary, we will try to further elucidate the possibility of the involvement of IL-33 in the onset of breast cancer in schizophrenia patients.

BREAST CANCER RISK AND SCHIZOPHRENIA

Disturbingly, approximately 2.1 million new cases of breast cancer were diagnosed worldwide in 2018, accounting for nearly one in four cancers in women and resulting in approximately 630000 deaths[5]. Previous epidemiological studies suggest that breast cancer is more common in patients with severe mental disorders than in the general population[6,7]. Among mental illnesses, a higher incidence of breast cancer has been observed in schizophrenia than in mood disorders[8]. Patients with schizophrenia have an increased risk of breast cancer, but not cancer overall[9,10]. The mortality cancer risk in schizophrenia is estimated to be 40% higher than in the general population and 51% higher than in individuals without schizophrenia[11].

The aspects of genetics, as well as epigenetic disturbances due to unhealthy lifestyle and harmful habits should be considered in this comorbidity. Recently, the genetic overlap of schizophrenia and breast cancer has been extensively reported[12]. A study by Lu *et al*[3] reported the phenotypic and genetic positive association of schizophrenia and breast cancer, estimated the percentage of genetic overlap to be 0.14 [95% cumulative incidence (CI): 0.09-0.19], and identified a shared locus at *19p13* (*GATAD2A*) as a significant risk factor for the development of both diseases. A polymorphism of the breast cancer resistance protein transporter (*ABCG2*) was associated with a 4-fold higher probability of a relevant reduction in positive and negative schizophrenia syndrome[13]. This suggests a potential genetic overlap between the two diseases.

In recent years, epidemiological evidence of a controversial association between cancer and neurodegenerative diseases has been increasing. Common etiological factors may play opposing roles in the pathogenesis of neurodegeneration and breast cancer[14,15]. Characteristic brain pathology leads to neuronal cell death and neurodegeneration over time, whereas cancer is dominated by the process of unlimited cell proliferation[16,17]. Evidence suggests that common biological mechanisms such as oxidative stress, metabolic dysregulation and inflammation underlie both diseases, all of which could promote apoptosis and cell proliferation[18-20].

Some immune-metabolic specifiers observed in patients with schizophrenia, such as diabetes, hyperinsulinemia, insulin resistance, and hyperlipidemia, may also be involved in the development of breast cancer[21-23]. Inflammatory changes that occur in patients with schizophrenia could also be marked as a cancer risk factor[24] (Figure 1). IL-33 is significantly higher in serum, indicating tumor recurrence, which also indicates poor prognosis in patients with breast cancer[25-27]. Similarly, higher serum levels of IL-33 are measured in schizophrenia during psychotic episodes[4].

So far, many contributing risk factors have been considered for the onset of breast carcinoma, and they seem to overlap with those considered lifestyle-related qualifiers in patients with schizophrenia. Behavioral habits such as smoking, alcohol consumption, obesity, physical inactivity and stress exposure are considered hazardous in the etiology of breast carcinoma[28-31].

It is particularly important to acknowledge gender specificities in schizophrenia. Gender differences in breast carcinoma risk have been observed in people without mental illnesses, but also in patients with schizophrenia. Taiwanese women with schizophrenia were observed to have a 1.94-fold higher risk of breast cancer than non-schizophrenic controls[32]. In addition, hormonal disturbances have been implicated as a risk factor for schizophrenia and breast cancer. According to previous findings, estrogen levels in women decrease during certain periods of life, such as during menstruation, after childbirth, and menopause, which can often lead to an exacerbation of schizophrenia symptoms and resistance to antipsychotic treatment[33,34]. At the same time, estrogen intermediates carcinoma development[35].

IL-33 ROLE IN NEUROINFLAMMATION AND NEURODEGENERATION

IL-33 is a multifunctional cytokine, and an alarmin, a damage-associated molecular pattern (DAMP), an endogenous molecule released into the extracellular space upon cellular stress and damage. DAMPs can correct altered physiological states and regulate homeostasis at low concentrations, propagate inflammatory reactions at high concentrations, or even lead to trauma and activation of surrounding cells and recruitment of distant cells in excessive release[36]. The role of DAMPs in neurodegenerative diseases has already been recognized in sterile inflammation. As recently summarized by Pandolfo *et al*[37], acute or chronic stress may trigger sterile inflammation associated with DAMPs and may be an etiopathogenetic mechanism for affective disorders.

In recent years, there is increasing evidence for an important immunomodulatory role of IL-33 in neurodegenerative diseases. IL-33 is a multifunctional cytokine that acts intracellularly as a nuclear factor and extracellularly as a cytokine[38]. By binding to the trans-membranes full length receptor (sST2), IL-33 exerts its biological activity through the IL-33/suppressor of tumorigenicity 2 (ST2) signaling pathway[39]. In contrast, the soluble form functions as a decoy receptor and limits the biological activity of IL-33[40]. IL-33 is highly expressed in the brain and released from astrocytes and oligodendrocytes, while the ST2 receptor is expressed in glial cells[41]. It has a dual function and may exert pro-inflammatory or anti-inflammatory effects in the central nervous system (CNS)[42,43]. Up-regulated expression of IL-33 in peripheral cells contributes to blood-brain barrier disruption[44]. By binding to the ST2 receptor, IL-33 promotes microglial activation and proliferation and enhances production of different cytokines, leading to an acute inflammatory response[45]. IL-33 signaling is associated with regulatory T and B cell responses[46,47]. By inducing microglial and macrophage polarization to an anti-inflammatory type 2 phenotype and phagocytosis, IL-33 exerts a neuroprotective and reparative role in the CNS[45,48].

In Alzheimer's disease (AD), soluble decoys trap IL-33 already produced at lower levels, and its concentrations in serum and cerebrospinal fluid are significantly reduced[49]. IL-33 could exert a neuroprotective effect by inducing innate immunity to reduce soluble amyloid β levels and amyloid plaque deposition[50]. Carlock *et al*[51] in 2017 pointed out that deficiency of IL-33 caused tau abnormality and late-onset

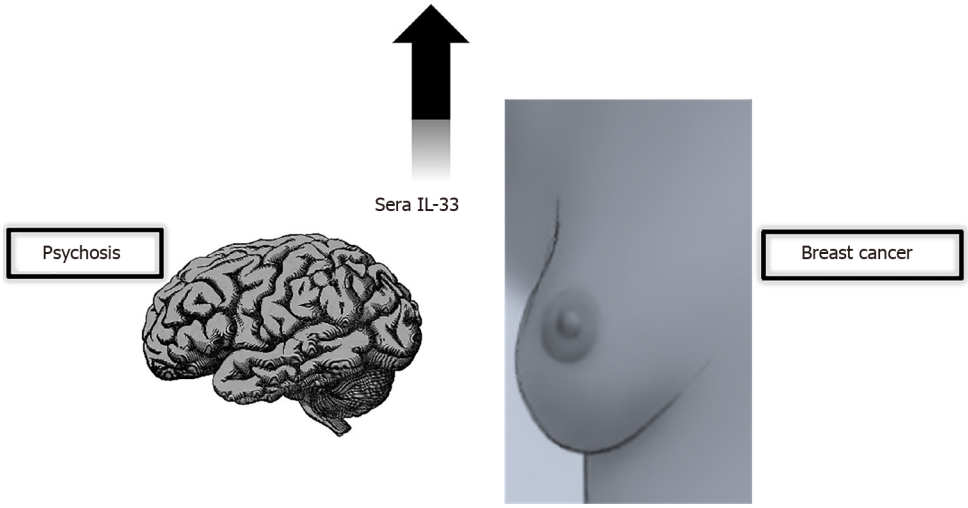


Figure 1 Interleukin-33/suppressor of tumorigenicity 2 axis as a crossroad in schizophrenia-breast cancer comorbidity. Higher serum levels of interleukin-33 (IL-33) have been measured in a psychotic episode of schizophrenia, and IL-33 is also significantly higher in serum and portends tumor recurrence in patients with breast cancer. IL-33: Interleukin-33.

neurodegeneration in the cerebral cortex and hippocampus, accompanied by memory impairment. A recent study suggested that IL-33 gene mutations affect susceptibility to late-onset AD, which in turn confirms that IL-33 may exacerbate neuroinflammation and cognitive decline[52,53].

As a neuroinflammatory and neurodegenerative disease, multiple sclerosis (MS) is associated with increased expression of IL-33 in the periphery, white matter, and plaque areas of the MS brain[54-57]. However, the exact role of IL-33 has not been fully elucidated, and data in the current literature are inconsistent. Previous studies have supported the involvement of IL-33 as a proinflammatory cytokine in disease pathology[56]. However, several recent observations suggest a dominant neuroreparative role of IL-33 in MS. Studies on experimental autoimmune encephalomyelitis (EAE) reported a detrimental effect of IL-33 treatment on EAE severity. The identification of ST2 expression by oligodendrocytes indicates an important role in the myelination process during CNS development and the repair phase of MS[57,58].

Recently, the protective effect of IL-33 in some acute neurological states has been reported. For example, Miao *et al*[59] in 2021 highlighted that increased IL-33 levels might reduce brain damage in patients with intracerebral hemorrhage. The reviewed results support the evidence of elevated IL-33 serum levels in the acutisation of schizophrenia and depression, suggesting the involvement of this axis in the processes of relapse and recurrence of mental disorder[37].

IL-33 ROLE IN CANCEROGENESIS

IL-33 exerts its function by binding to the ST2 receptor, expressed on T helper (Th) 2 cells, but skewing toward Th1 cytokines has been found in MS[60,61]. IL-33 has been categorized as a promoter of Th2 immunity by inducing the production of IL-4, IL-5 and IL-13, M2 polarization of macrophages, and eosinophil recruitment[62]. The Th2-related cytokine can act as a pro-tumorigenic factor by limiting anti-tumor immunity and promoting extracellular matrix remodeling, but the localization of IL-33 is crucial for accurately distinguishing its effect in tumor biology[63].

IL-33 stimulates innate type 2 lymphoid cells (ILC2s), leading to the release of proinflammatory cytokines and type-2 inflammation[64]. An association with allergic disease has been observed in patients with autism spectrum disorder, and an immune pattern initiated by IL-33, ILC2 and mast cells has been confirmed[65]. To date, there are no data on the role of ILC2s in schizophrenia, and these findings in autism spectrum disorder as a neurodegenerative disease may serve as a basis for further investigation in psychosis. ILC2s are the largest subset in the lung and skin associated with pro-allergic and antiparasitic immunity. Dysregulation of their signaling circuitry may accelerate fibrotic responses and have predominantly carcinogenic activities[66]. In the breast cancer model, increased endogenous IL-33 was observed during cancer progression, further facilitating the intratumoral accumulation of immunosuppressive

IL-13-producing innate lymphoid cells and promoting the growth of breast cancer and metastases in the lungs[67]. Escalation of systemic IL-33 secretion could precipitate the carcinoma development in neurodegenerative diseases and schizophrenia as a representative.

IL-33 IN THERAPEUTIC STRATEGIES FOR BREAST CANCER IN SCHIZOPHENIA

The first line of treatment for schizophrenia is antipsychotics, but nowadays it is surprising that these drugs could also have anticancer effects[68]. Previous studies have shown that some antipsychotics may cause higher prolactin levels, called "prolactin-raising", and thus an increased risk of breast cancer by promoting carcinogenesis and transition to invasive carcinoma[69]. Breast cancer risk was higher in patients receiving first-generation antipsychotics and second-generation antipsychotics alone, as well as a combination of both, regardless of the mean exposure dose[32]. However, it must be emphasized that according to the World Federation of Societies of Biological Psychiatry, breast cancer is not listed as an antipsychotic-induced hyperprolactinemia adverse effect[70]. De Hert *et al*[71] reported that studies in patients with idiopathic hyperprolactinemia, prolactinomas, and Parkinson's disease (PD) found no carcinogenic effects of prolactin. Hoehn *et al*[72] first described the possible inverse association between PD and neoplasms. This may suggest that excessive dopamine or prolactin release is not the exclusive mechanism leading to breast cancer development, but rather a milieu for more complex interactions. Our study exploring the impact of risperidone and paliperidone as prolactin-raising long-acting injections suggested a decrease in IL-33 serum levels in patients with schizophrenia in remission with possibly balancing and antitumorigenic properties[4].

The clinical presentation of schizophrenia differs in men and women and could be partly attributed to the neuroprotective properties of estrogens[73]. Modulation of dopamine 2 receptor occupancy of antipsychotics can also be associated with estrogens [74]. Estrogens protect women from infections and prevent mortality associated with inflammation by downregulating levels of pro-inflammatory cytokines IL-1β, IL-10, and tumor necrosis factor alpha[75].

Selective estrogen receptor modulators such as raloxifene have an antiestrogenic effect in the breast and uterus, but not in the brain and bone tissue[76]. Of particular interest to us was that raloxifene was not only effective in improving schizophrenia, but even more effective in improving cognitive symptoms in postmenopausal women with low estrogen levels[77,78] (Figure 2A). This tissue-specific dual action of the drug could be simultaneously used for targeted breast cancer therapy and mental state in schizophrenia patients and specifically explored in the context of IL-33 secretion.

Guidelines recommend tamoxifen as a standard of care for premenopausal women for 5-10 years[79]. *In vitro* studies could guide further investigations on the beneficial properties of the prolactin-elevating antipsychotics thioridazine and chlorpromazine in enhancing the effect of tamoxifen in tamoxifen-resistant human breast cancer cells [80]. IL-33 overexpression in breast cancer cells results in resistance to tamoxifen-induced tumor growth inhibition, while IL-33 knockdown corrects this problem[81]. This knockdown could be achieved through the action of antipsychotics (Figure 2B).

CONCLUSION

Individualized treatment is of great importance in modern medicine, as patients with schizophrenia must be treated equally. Diagnosis and treatment of somatic states in schizophrenia patients could influence behavioral changes and improve outcome. Prevention strategies for breast carcinoma onset in schizophrenia patients could be developed by understanding and recognizing the genetic background, lifestyle, and individual factors, altogether resulting in phase-specific immune dysregulation. IL-33 as a marker of innate immunity and an alarmin has been discussed in other neurodegenerative diseases. Further exploration of IL-33 as an alarmin in mental disorders should take into account gender, age at onset, duration of illness, frequency of disease acutisation, antipsychotic treatment, and a variety of comorbid somatic states including breast cancer. There appears to be an impact on the occurrence of positive symptoms and exacerbation of schizophrenia, but also on the progression of breast cancer, making IL-33 a candidate for centered therapy. We have shown that

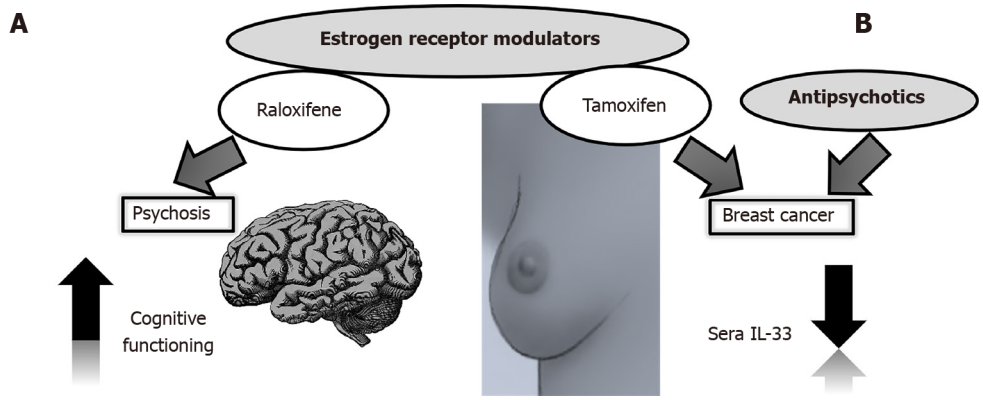


Figure 2 Estrogen receptor modulators and antipsychotics in interleukin-33 targeting strategies. A: Raloxifene could be tissue-specific and improve cognition. B: Tamoxifen resistance in breast carcinoma could be improved by antipsychotics targeting IL-33. IL-33: Interleukin-33.

antipsychotics with their anticarcinogenic properties could be beneficial, possibly through prolactin elevation, tissue-specific estrogen-sparing drugs, and additional IL-33 downregulation.

ACKNOWLEDGEMENTS

This review was enriched by the valuable collaboration with the Center for Molecular Medicine and Stem Cell Research, at the Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia. We would like to thank Bojana Mircetic for language editing.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 1075-1094

DOI: 10.5498/wjp.v11.i11.1075

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Basic Study

CPEB1, a novel risk gene in recent-onset schizophrenia, contributes to mitochondrial complex I defect caused by a defective provirus ERVWE1

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Author contributions: Xia YR designed and performed the experiments and wrote the manuscript; Yan QJ and Wu XL contributed to data collection; Yao W and Li XH performed some of the cytological experiments; Li WS and Wei XC conducted the data analyses; Zhu F served on the scientific advisory board for the School of Medicine, Wuhan University, conceived the study, was in charge of the overall direction and planning, drafted the manuscript, and the paid bills for this procedure.

Institutional review board statement: The protocol of this study was approved by the Institutional Review Board of Wuhan University, School of Basic Medical Sciences, and the study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments

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Abstract

BACKGROUND

Schizophrenia afflicts 1% of the world population. Clinical studies suggest that schizophrenia patients may have an imbalance of mitochondrial energy metabolism *via* inhibition of mitochondrial complex I activity. Moreover, recent studies have shown that ERVWE1 is also a risk factor for schizophrenia. Nevertheless, there is no available literature concerning the relationship between complex I deficits and ERVWE1 in schizophrenia. Identifying risk factors and blood-based biomarkers for schizophrenia may provide new guidelines for early interventions and prevention programs.

AIM

To address novel potential risk factors and the underlying mechanisms of mitochondrial complex I deficiency caused by ERVWE1 in schizophrenia.

METHODS

Quantitative polymerase chain reaction (qPCR) and enzyme-linked immunosorbent assay were used to detect differentially expressed risk factors in blood samples. Clinical statistical analyses were performed by median analyses and Mann-Whitney U analyses. Spearman's rank correlation was applied to examine the correlation between different risk factors in blood samples. qPCR, western blot analysis, and luciferase assay were performed to confirm the relationship among ERVWE1, cytoplasmic polyadenylation element-binding protein 1 (CPEB1), NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2), and NDUFV2 pseudogene (NDUFV2P1). The complex I enzyme activity microplate assay was

involving humans. Informed consent was obtained for experimentation with human subjects and their privacy rights were always observed.

Conflict-of-interest statement: No potential conflicts of interest.

Data sharing statement: The data used and analyzed during the current study are available from the corresponding author upon request.

Supported by the National Natural Science Foundation of China, No. 81971943, No. 81772196, No. 31470264, No. 81271820, No. 30870789, and No. 30300117; the Stanley Foundation of United States, No. 06R-1366 (for Zhu F); and the Medical Science Advancement Program (Basic Medical Sciences) of Wuhan University, No. TFJC 2018002.

Country/Territory of origin: China

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: April 25, 2021
Peer-review started: April 25, 2021

carried out to evaluate the complex I activity induced by ERVWE1.

RESULTS
Herein, we reported decreasing levels of CPEB1 and NDUFV2 in schizophrenia patients. Further studies showed that ERVWE1 was negatively correlated with CPEB1 and NDUFV2 in schizophrenia. Moreover, NDUFV2P1 was increased and demonstrated a significant positive correlation with ERVWE1 and a negative correlation with NDUFV2 in schizophrenia. *In vitro* experiments disclosed that ERVWE1 suppressed NDUFV2 expression and promoter activity by increasing NDUFV2P1 level. The luciferase assay revealed that ERVWE1 could enhance the promoter activity of NDUFV2P1. Additionally, ERVWE1 downregulated the expression of CPEB1 by suppressing the promoter activity, and the 400 base pair sequence at the 3′ terminus of the promoter was the minimum sequence required. Advanced studies showed that CPEB1 participated in regulating the NDUFV2P1/NDUFV2 axis mediated by ERVWE1. Finally, we found that ERVWE1 inhibited complex I activity in SH-SY5Y cells *via* the CPEB1/NDUFV2P1/NDUFV2 signaling pathway.

CONCLUSION
In conclusion, CPEB1 and NDUFV2 might be novel potential blood-based biomarkers and pathogenic factors in schizophrenia. Our findings also reveal a novel mechanism of ERVWE1 in the etiology of schizophrenia.

Key Words: ERVWE1; CPEB1; NADH dehydrogenase ubiquinone flavoprotein 2; complex I; Pseudogene

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Core Tip: Schizophrenia is a devastating psychiatric disorder. Clinical studies suggest complex I deficits and abnormal expression of ERVWE1 in schizophrenia. We found that CPEB1 might be a novel blood-based biomarker for schizophrenia. Analyses indicated that ERVWE1 was negatively correlated with CPEB1 and NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) in schizophrenia patients. CPEB1 functioned as a mediator of the NDUFV2 pseudogene (NDUFV2P1)/NDUFV2 pathway induced by ERVWE1. Moreover, ERVWE1 inhibited complex I activity *via* the CPEB1/NDUFV2P1/NDUFV2 pathway. Thus, CPEB1 and NDUFV2 may be independent risk factors for schizophrenia. Our findings also reveal the role of ERVWE1 in modulating mitochondrial energy metabolism in schizophrenia.

Citation: Xia YR, Wei XC, Li WS, Yan QJ, Wu XL, Yao W, Li XH, Zhu F. CPEB1, a novel risk gene in recent-onset schizophrenia, contributes to mitochondrial complex I defect caused by a defective provirus ERVWE1. *World J Psychiatr* 2021; 11(11): 1075-1094
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1075.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1075

INTRODUCTION

Schizophrenia is a chronic brain disorder with a worldwide prevalence of approximately 1%[1]. It causes many symptoms including hallucinations, delusions, breaking from reality, and a lack of motivation[2]. Schizophrenia imposes a financial burden on society because of high indirect costs[3]. There are numerous hypotheses about schizophrenia. One of the currently prevailing hypothesis proposes that mitochondrial metabolic dysfunction[4-6] is strongly involved in the pathophysiology of schizophrenia. Mitochondrial complex I deficiency is the most frequent cause of mitochondrial metabolic dysfunction implicated in the development of schizophrenia[7-9]. The mitochondrial oxidative phosphorylation (OXPHOS) system comprises five multimeric protein complexes, and plays a central role in cellular energy metabolism. Complex I is the first entry point of electrons into the respiratory chain and is suggested as the rate-limiting step in OXPHOS. NADH dehydrogenase ubiquinone

First decision: July 14, 2021
Revised: July 26, 2021
Accepted: August 25, 2021
Article in press: August 25, 2021
Published online: November 19, 2021

P-Reviewer: Pethe P
S-Editor: Wu YXJ
L-Editor: Filipodia
P-Editor: Guo X



flavoprotein 2 (NDUFV2) assembles in the catalytic component of complex I. Ample evidence has revealed that NDUFV2 is a candidate gene for schizophrenia[10-12]. NDUFV2 pseudogene (NDUFV2P1), an inactive locus of the NDUFV2 subunit of the complex I[13], has increased expression in schizophrenia-derived cells[14]. Knockout of CPEB1, a sequence-specific RNA-binding protein[15], reduces NDUFV2 protein expression and inhibits complex I activity in mice[16]. Nonetheless, there is no definitive hypothesis on the pathogenesis of schizophrenia.

Human endogenous retroviruses (HERVs), which comprise about 8% of the human genome, have emerged as novel risk factors for schizophrenia[17-19]. As remnants of ancient retroviral infections, most HERVs have acquired inactivating mutations during evolution[20]. In some instances, some HERVs sequences remain dormant functional copies encoding retroviral proteins[21] and play an active role in human placental development and the innate immune system. HERVs possess a similar genome structure as typical exogenous retroviruses and are composed of gag, pol, and env regions sandwiched between two long terminal repeats[21]. Conventionally, based on sequence similarity with their exogenous retrovirus, HERVs are divided into three classes: class I (gamma-retroviruses), class II (beta-retroviruses), and class III (spuma-retroviruses)[22].

The HERV W family (HERV-W), the oldest group of HERVs, belongs to class I transposable elements. ERVWE1, HERV-W-derived envelope proteins at chromosome 7, is also known as HERV-W env or Syncytin-1[23]. ERVWE1 is a cell-cell fusion glycoprotein that is usually expressed on the surface of cytotrophoblasts and syncytiotrophoblast. It mediates trophoblast fusion[24] and blocks maternal immune[25], which are essential for normal placental development. ERVWE1 is aberrantly expressed in schizophrenia[18,19,26]. Results from our previous study showed that ERVWE1 is significantly increased in the plasma of recent-onset schizophrenia patients[18,19]. Perron *et al*[26] also reported antigenemia of ERVWE1 was elevated in the serum of schizophrenic patients.

Both complex I deficiency and ERVWE1 are risk factors for developing schizophrenia. However, no detailed study has been performed on the cytoplasmic polyadenylation element-binding protein 1 (CPEB1) expression profile in schizophrenia. Furthermore, the relationships among these factors in schizophrenia remain unknown. In this study, we found that CPEB1 protein was decreased and negatively correlated with ERVWE1 in recent-onset schizophrenia patients. Quantitative polymerase chain reaction (qPCR) and enzyme-linked immunosorbent assay (ELISA) showed a significant reduction of NDUFV2 in schizophrenia. We further demonstrated the increased levels and positive correlation between ERVWE1 and NDUFV2P1 in schizophrenia patients. Moreover, the mRNA level of ERVWE1 and NDUFV2P1 was negatively correlated with NDUFV2 protein expression in schizophrenia patients. A series of cell and molecular biology experiments were used to reveal the relationship among CPEB1, NDUFV2P1/NDUFV2, ERVWE1, and complex I deficiency. The results suggested that ERVWE1 could decrease the mRNA and protein expression of NDUFV2 and suppress NDUFV2 promoter activation by increasing NDUFV2P1 transcript levels. The luciferase assay showed that overexpression of ERVWE1 enhanced NDUFV2P1 promoter activity. ERVWE1 also inhibited CPEB1 mRNA and protein expression by regulating its promoter. Moreover, CPEB1 was essential in the NDUFV2P1/NDUFV2 axis triggered by ERVWE1 in SH-SY5Y cells. Finally, ERVWE1 induced complex I inactivation *via* the CPEB1/NDUFV2P1/NDUFV2 signaling pathway in SH-SY5Y cells.

In summary, CPEB1 and NDUFV2 might be novel schizophrenia risk factors. To the best of our knowledge, no similar observations have been published to date. Moreover, our results indicated that ERVWE1 abolished complex I activity by regulating parental- and pseudo-NDUFV2 genes *via* suppressing CPEB1 in schizophrenia. Our findings might provide new insights into how ERVWE1 impairs mitochondrial energy metabolism and contributes to the pathogenesis of schizophrenia.

MATERIALS AND METHODS

Blood samples

Blood samples from patients and normal individuals, including whole peripheral blood for RNA isolation and serum for ELISA analyses, were collected from the Renmin Hospital, Wuhan University (Wuhan, China). All patients with recent-onset schizophrenia met the Diagnostic and Statistical Manual of Mental Disorders, 4th

Edition criteria. None of the patients had a history of psychiatric illness. Informed written consent was obtained from all subjects, and the study was approved by the Institutional Review Board of Wuhan University, School of Basic Medical Sciences. All samples were preserved at -80°C before utilization. There were no significant differences in median age, education, body mass index, smoking status, and sex between control and schizophrenia patients. Demographics are presented in Supplementary Tables 1 and 2.

Plasmid construction

The pCMV-ERVWE1 plasmid was constructed as previously described[18]. Human CPEB1 (NM_030594.5) and NDUFV2P1 (NC_000019.10:c53224879-53223909) genes were amplified separately according to sequences of these genes in National Center for Biotechnology Information (Bethesda, MD, United States). The promoters of human CPEB1 (-800 to 0, -600 to 0, -400 to 0, and -200 to 0), NDUFV2 (-1100 to +100), and NDUFV2P1 (-900 to 0) were cloned into the luciferase reporter vector pGL3-basic, which contains a firefly luciferase gene. All primers were designed using Primer premier 5.0 and described in Supplementary Table 3.

One short hairpin RNA (shRNA) targeting NDUFV2P1 (shNDUFV2P1, 5′-CCAAGGAGTGGACGCTTCT-3′) and the control shRNA (sh-Control, 5′-CCAAGTGGGCACGTAGTCT-3′) were cloned into the pSilencer 2.1-U6 neo shRNA expression vector (AM5764; Ambion Inc., Austin, TX, United States). All of the constructs were confirmed by sequencing (Sangon Biotech, Shanghai, China).

Cell culture and transfection

SH-SY5Y (CRL-2266) human neuroblastoma cells were obtained from American Type Culture Collection. SH-SY5Y cells were cultured in a 1:1 mixture of minimum essential medium (2225320; Gibco, Gaithersburg, MD, United States) and F-12 nutrient mixture (2209586; Gibco). All media were supplemented with 10% fetal bovine serum (2001003, Biological Industries, Beit HaEmek, Israel), 1% penicillin-streptomycin (2211093; Gibco) and 1% sodium pyruvate (2185865; Gibco) under 5% CO_2 at 37 °C. Transfection was performed with Lipofectamine 2000 transfection reagent (11668-019; Invitrogen, Carlsbad, CA, United States) according to the manufacturer's instructions. Cells were incubated for further analyses after 24, 36, and 48 h post-transfection.

RNA extraction and reverse transcription

Total blood RNA was extracted from whole blood according to the standard protocols for TRIzol LS reagent (10296028; Invitrogen). Total cellular RNA was isolated with TRIzol reagent (15596018; Invitrogen), followed by chloroform separation and isopropanol precipitation. Then, 1 μg total RNA samples were reverse-transcribed into cDNA using the ReverTra Ace qPCR RT master mix with gDNA remover (FSQ-301; Toyobo, Osaka, Japan) according to the manufacturer's recommendations.

Quantitative PCR

The mRNA levels were measured by quantitative PCR (qPCR) utilizing the 2x Sybr Green qPCR mix (2992239AX; Aidlab Biotechnologies Co. Ltd., Beijing, China) using a mini opticon detector (Bio-Rad, Hercules, CA, United States). GAPDH was used as an internal control, and the relative mRNA expression was calculated using the $2^{-\Delta\Delta Ct}$ method. The primers were designed according to gene sequences in NCBI using primer premier 5.0, and are listed in Supplementary Table 4.

Protein extraction and western blot analysis

Cultured cells were homogenized and lysed in M-PER TM mammalian protein extraction reagent (UC282138; Thermo Fisher Scientific, Waltham, MA, United States) containing protease and phosphatase inhibitors (Roche Applied Science, Indianapolis, IN, United States). Protein concentrations were quantified using the Pierce TM BCA Protein Assay (UD281372; Thermo Fisher Scientific). Protein samples were loaded onto a 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and was then electrotransferred to a PVDF membrane (IPVH00010; Amersham Biosciences, Piscataway, NJ, United States). The following antibodies purchased from ABclonal Technology (Woburn, MA, United States) were used in this study: rabbit anti-ERVWE1 antibody (dilution 1:1000, A16522), rabbit anti-CPEB1 antibody (dilution 1:1000, A5913), rabbit anti-NDUFV2 antibody (dilution 1:1500, A7442), mouse anti-GAPDH antibody (dilution 1:50000, AC002), goat anti-mouse IgG-horseradish peroxidase (HRP) (dilution 1:5000, AS003), and goat anti-rabbit IgG-HRP (dilution 1:5000, AS014). The bands were visualized using the Millipore Immobilon Western

Chemiluminescent HRP Substrate (WBKLS0500; Millipore, Burlington, MA, United States). Images were captured using the Tanon 5200 chemiluminescence imaging system (Tanon, Shanghai, China). Target protein expression levels were normalized to GAPDH.

Luciferase assay

The luciferase activity was carried out using the Dual-Luciferase Assay System (E1960; Promega, Madison, WI, United States) in accordance with the manufacturer's protocol. Firefly luciferase activity was normalized to pRL-CMV Renilla luciferase activity. The promoter activity is expressed as the mean ± standard deviation (SD) of at least triplicate replicates.

ELISA

The expression levels of human CPEB1 (072020; Huaer Biotech Co. Ltd, Wuhan, China) and NDUFV2 (202103; Meiman Industrial Co. Ltd, Jiangsu, China) in serum were measured by an ELISA kit according to the manufacturer's recommendations. Absorbance was measured at 450 nm using a spectrophotometer (Thermo Fisher Scientific). The concentrations of CPEB1 and NDUFV2 were determined by comparing the optical density of the samples to the standard curve.

Analyses of mitochondrial OXPHOS complex I activity

Mitochondrial OXPHOS complex I activity was detected by the Immunocapture ELISA Kit following the manufacturer's instructions (AB109721; Abcam, Cambridge, United Kingdom). After cells were lysed with detergent solution, protein concentration was adjusted to 1 mg/mL in incubation solution. The diluted 200 μL sample and control were loaded onto the wells of a microplate pre-coated with complex I capture antibody for 3 h at room temperature. Complex I activity was determined by measuring the oxidation of NADH to NAD^+ and simultaneous reduction of a dye, which leads to increased absorbance at 450 nm. The activity was expressed as the change in absorbance per min using this equation: complex I activity = [Abs 1 – Abs 2] / [Time 1 – Time 2].

Statistical analyses

SPSS and GraphPad Prism were used for the statistical analyses. For the blood sample results, the median analyses and Mann-Whitney U analyses were performed to compare the different expressions of ERVWE1, CPEB1, NDUFV2P1, and NDUFV2 between the schizophrenia and control groups. Correlation analyses were performed using the Spearman's rank correlation. All data were obtained from at least three independent experiments and presented as the mean ± SD. Statistical and data analyses were performed by one-way analysis of variance and Student's *t*-tests. Significance was considered at $P < 0.05$.

RESULTS

Degradation of CPEB1 and NDUFV2 proteins and the correlation among ERVWE1, NDUFV2, and NDUFV2P1 in schizophrenia

Many biomarkers in serum have been studied to determine whether they can help diagnose schizophrenia. A genome-wide association study (GWAS) identified CPEB1 as a new susceptibility locus for schizophrenia[27]. Nevertheless, there has been no report on the expression of CPEB1 in patients with schizophrenia. Here, we showed that CPEB1 was significantly downregulated in schizophrenia compared to healthy people in blood samples using ELISA ($P < 0.05$; Figure 1A and Table 1). We further found decreased mRNA and protein levels of NDUFV2 in schizophrenia patients ($P < 0.05$, Figure 1B; $P < 0.01$, Figure 1C and Table 2). NDUFV2P1 (NDUFV2 pseudogene) was significantly upregulated in schizophrenia patients ($P < 0.01$; Figure 1D). We also found increased ERVWE1 mRNA expression in schizophrenia patients ($P < 0.01$; Figure 1E). Correlation analyses through linear regression revealed that ERVWE1 mRNA was negatively correlated with CPEB1 ($P < 0.001$; Figure 1F) and NDUFV2 protein ($P < 0.001$; Figure 1G), and positively correlated with NDUFV2P1 transcripts ($P < 0.001$; Figure 1H) in schizophrenia. Moreover, high levels of NDUFV2P1 mRNA were correlated with decreased NDUFV2 protein in schizophrenia ($P < 0.001$; Figure 1I). Univariate and multivariate analyses identified CPEB1 and NDUFV2 as two possible independent risk factors for schizophrenia (Supplementary Table 5).

Table 1 The concentration of CPEB1 in the blood of control and schizophrenia patients

Control	*n*	38	Schizophrenia	*n*	41
	Mean	25.76		Mean	14.63
	Median	22.47		Median	16.19
	SD	11.70		SD	5.39
	Skewness	2.89		Skewness	-0.93
	SE of Skewness	0.38		SE of Skewness	0.37
	Range	53.26		Range	18.63
	Minimum	16.46		Minimum	2.14
	Maximum	69.70		Maximum	23.67

SD: Standard deviation; SE: Standard error.

Table 2 The concentration of NADH dehydrogenase ubiquinone flavoprotein 2 in the blood of control and schizophrenia patients

Control	*n*	38	Schizophrenia	*n*	41
	Mean	28.16		Mean	20.14
	Median	26.87		Median	20.51
	SD	11.02		SD	5.47
	Skewness	2.691		Skewness	-0.67
	SE of Skewness	0.38		SE of Skewness	0.37
	Range	60.09		Range	23.23
	Minimum	15.76		Minimum	4.91
	Maximum	75.85		Maximum	28.14

SD: Standard deviation; SE: Standard error.

In summary, CPEB1 and NDUFV2 might be novel potential blood-based biomarkers and possible pathogenic factors for schizophrenia, and are negatively correlated with ERVWE1 in schizophrenia.

ERVWE1 reduces the expression of NDUFV2 by upregulating NDUFV2P1.

The clinical data showed a significant correlation among ERVWE1, NDUFV2P1, and NDUFV2 gene expression in schizophrenia. Thus, to evaluate the causal relationship among ERVWE1, NDUFV2P1, and NDUFV2, experiments were performed in human neuroblastoma cells. ERVWE1 expression in transfected cells was detected by qPCR and western blotting (Supplementary Figure 1A and B). The mRNA level of NDUFV2P1 was significantly increased in SH-SY5Y cells after overexpression of ERVWE1 ($P < 0.05$; Figure 2A). Luciferase assays showed that overexpression of ERVWE1 greatly enhanced NDUFV2P1 promoter activity in SH-SY5Y cells ($P < 0.01$; Figure 2B). NDUFV2 is the parental gene of NDUFV2P1[13]. We found that ERVWE1 decreased both the mRNA ($P < 0.05$; Figure 2C) and protein levels of NDUFV2 in SH-SY5Y cells ($P < 0.05$; Figure 2D). Moreover, ERVWE1 reduced the expression of NDUFV2 by suppressing promoter activity in SH-SY5Y cells ($P < 0.01$; Figure 2E). These findings suggest that ERVWE1 downregulates the expression of NDUFV2 while upregulating its pseudogene, NDUFV2P1, in SH-SY5Y cells.

Pseudogene transcripts usually regulate the expression of their parental genes[28]. As shown in Figure 3A, the mRNA levels of NDUFV2 were significantly decreased in the NDUFV2P1 (+) group compared with the control ($P < 0.05$). Consistently, western blot analysis also confirmed that NDUFV2P1 inhibited the expression levels of NDUFV2 in SH-SY5Y cells ($P < 0.05$; Figure 3B). NDUFV2P1 expression in transfected cells was detected by qPCR (Supplementary Figure 2).

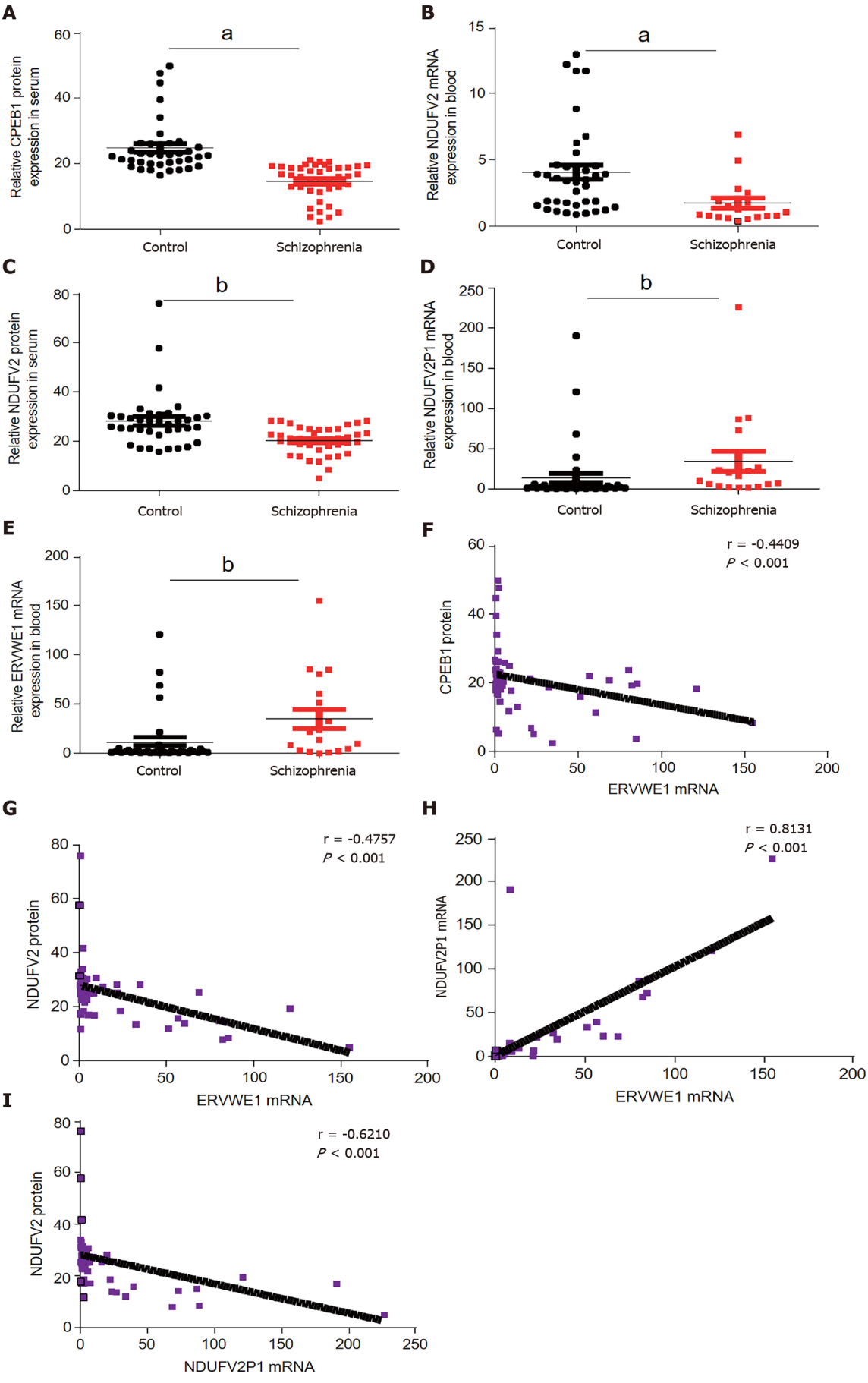


Figure 1 Cytoplasmic polyadenylation element-binding protein 1 (CPEB1) and NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2)

deficiency and the correlation among ERVWE1, CPEB1, NDUFV2, and NDUFV2 pseudogene (NDUFV2P1) in schizophrenia patients. A and C: Respectively represent the protein expression of cytoplasmic polyadenylation element-binding protein 1 (CPEB1) and NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) in the schizophrenia patients (n = 41) and in the control groups (n = 38) using enzyme-linked immunosorbent; B, D, and E: Respectively represent the mRNA levels of NDUFV2, NDUFV2 pseudogene (NDUFV2P1), and ERVWE1 in schizophrenia patients (n = 19) and the control groups (n = 38) using quantitative polymerase chain reaction; F: Correlation between ERVWE1 mRNA levels and CPEB1 protein levels in patients with schizophrenia and control groups (n = 57), where Y is the protein expression for CPEB1 and X is ERVWE1 mRNA value for each sample; G: Correlation between ERVWE1 mRNA levels and NDUFV2 protein levels in patients with schizophrenia and control groups (n = 57), where Y is the protein expression for NDUFV2 and X is ERVWE1 mRNA value for each sample; H: Correlation between ERVWE1 and NDUFV2P1 mRNA levels in patients with schizophrenia and control groups (n = 57), where Y is the mRNA expression for NDUFV2P1 and X is ERVWE1 mRNA value for each sample; I: Correlation between NDUFV2P1 mRNA levels and NDUFV2 protein levels in patients with schizophrenia and control groups (n = 57), where Y is the protein expression for NDUFV2 and X is NDUFV2P1 mRNA value for each sample. $^{a}P < 0.05$; $^{b}P < 0.01$.

To further explore whether NDUFV2P1 mediated the regulatory effect of ERVWE1 on the expression of NDUFV2, the shNDUFV2P1 plasmid was constructed. Knockdown of NDUFV2P1 substantially elevated the ERVWE1-induced mRNA expressions of NDUFV2 in SH-SY5Y cells ($P < 0.05$; Figure 3C). Moreover, western blotting showed similar results of increased NDUFV2 protein expression after NDUFV2P1 knockdown ($P < 0.05$; Figure 3D). Hence, these data demonstrated that ERVWE1 could mediate the downregulation of NDUFV2 by upregulating NDUFV2P1 in SH-SY5Y cells.

We further examined whether NDUFV2P1 had an effect on NDUFV2 promoter activity. Luciferase assays indicated that NDUFV2P1 inhibited NDUFV2 promoter activity ($P < 0.05$; Figure 3E) in SH-SY5Y cells. To explore the role of NDUFV2P1 in the ERVWE1-induced promoter activity of NDUFV2, shNDUFV2P1 was used. The reduced promoter activity was significantly recovered after knockdown of NDUFV2P1 ($P < 0.01$; Figure 3F), suggesting that ERVWE1 suppressed NDUFV2 promoter by elevating NDUFV2P1 transcript.

ERVWE1 mediates NDUFV2P1/NDUFV2 signaling pathway through the regulation of CPEB1

Our clinical data revealed CPEB1 was downregulated, and demonstrated a negative correlation between CPEB1 and ERVWE1 in schizophrenia patients. It would be intriguing to assess the effect of ERVWE1 on CPEB1. We found that both mRNA ($P < 0.01$; Figure 4A) and protein ($P < 0.05$; Figure 4B) expression of CPEB1 was significantly lower after overexpression of ERVWE1 in SH-SY5Y cells than in control cells. Moreover, the luciferase assay demonstrated that ERVWE1 suppressed the promoter activity of CPEB1 ($P < 0.01$; Figure 4C). In order to define the minimum sequence essential for the transcriptional control of CPEB1 gene, four sequentially truncated promoters were examined in transfection assay. The luciferase reporter assay demonstrated that the promoter ranged from -400 to 0 was the minimum sequence required for biological activity ($P < 0.05$; Figure 4D). Furthermore, we found that CPEB1 could downregulate NDUFV2P1 mRNA levels in SH-SY5Y cells ($P < 0.05$; Figure 4E). qPCR and western blot analysis confirmed CPEB1 transfection (Supplementary Figure 3A and B). Additionally, overexpression of CPEB1 substantially impaired the ERVWE1-induced mRNA expression of NDUFV2P1 in SH-SY5Y cells, suggesting that ERVWE1-induced NDUFV2P1 was mediated by CPEB1 ($P < 0.05$; Figure 4F).

Several studies have reported that CPEB1 regulates NDUFV2 expression by a post-transcriptional mechanism[16]. We also found no change in the mRNA expression of NDUFV2 after transfection with CPEB1 (Figure 5A). Western blotting showed that CPEB1 elevated the protein levels of NDUFV2 ($P < 0.01$; Figure 5B). We further assessed the possible role of CPEB1 in ERVWE1-mediated NDUFV2 expression. Our results revealed that NDUFV2 mRNA was not altered, regardless of whether CPEB1 was overexpressed compared with control cells (Figure 5C). Regardless of whether CPEB1 was highly expressed, western blot analyses revealed that CPEB1 could relieve the inhibitory effect of ERVWE1 on NDUFV2 ($P < 0.05$; Figure 5D). Together, these results suggest that ERVWE1 regulates the NDUFV2P1/NDUFV2 signaling pathway through the suppression of CPEB1.

ERVWE1 impairs electron transport chain complex I activity via the CPEB1/NDUFV2P1/NDUFV2 signaling pathway

NDUFV2 is a subunit of mitochondrial complex I[11]. Our above results demonstrated that ERVWE1 significantly reduced the mRNA and protein expressions of NDUFV2. Thus, we further analyzed the impact of ERVWE1 on complex I activity. Successful

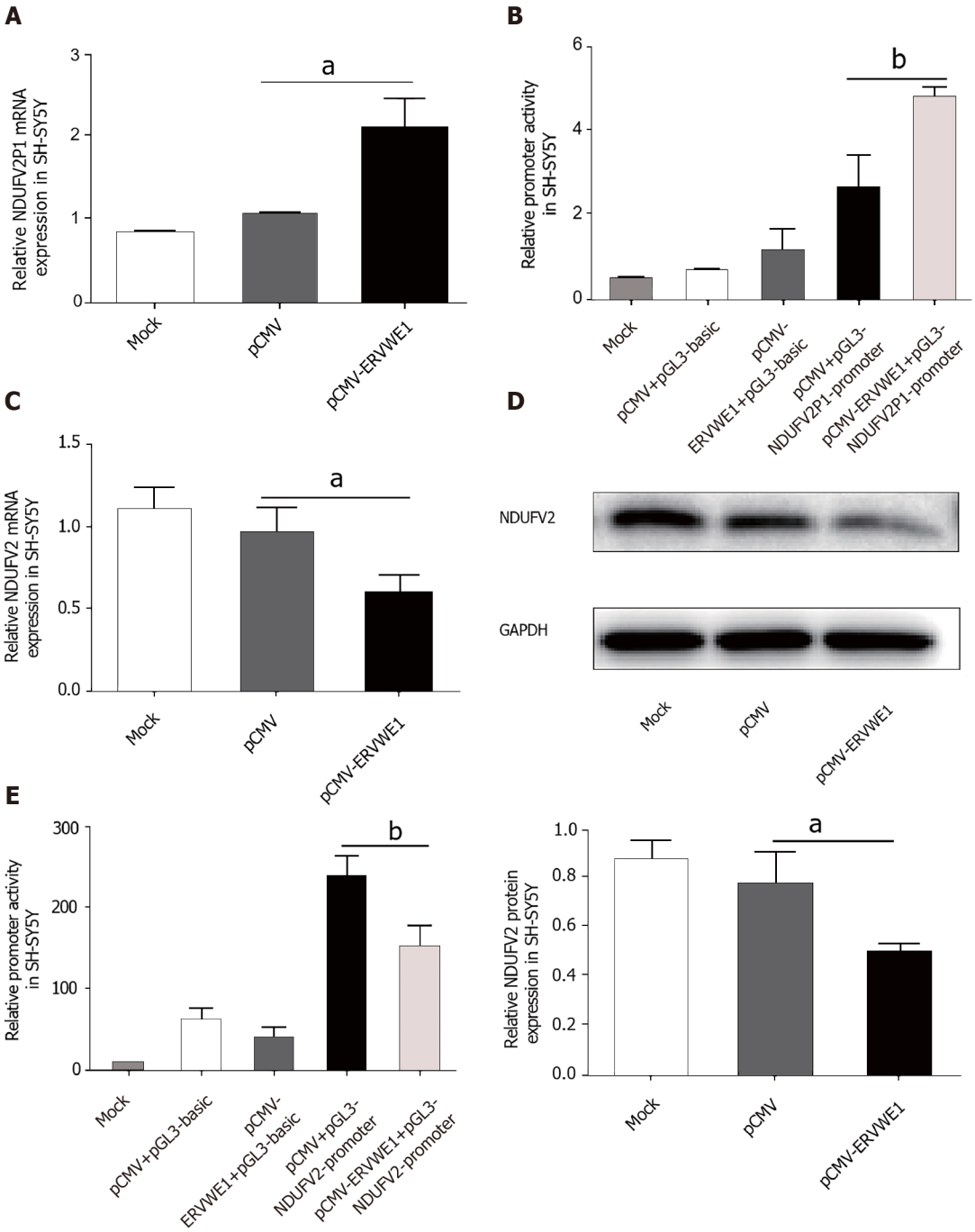


Figure 2 Overexpression of ERVWE1 elevated NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) pseudogene (NDUFV2P1) and reduced NDUFV2 levels. A and C: Respectively represent the mRNA levels of NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) pseudogene (NDUFV2P1) and NDUFV2 in ERVWE1-transfected SH-SY5Y cells using quantitative polymerase chain reaction; B: Luciferase assays of pGL3-NDUFV2P1 promoter co-transfected with pCMV-ERVWE1 or control vector in SH-SY5Y cells; D: Western blots of NDUFV2 and GAPDH in SH-SY5Y cells; E: Luciferase assays of pGL3-NDUFV2 promoter co-transfected with pCMV-ERVWE1 or control vector in SH-SY5Y cells. Each bar represents the mean ± SD of three independent experiments. [a]$P < 0.05$; [b]$P < 0.01$.

transfection was verified by western blot analyses in the transfected cells (Supplementary Figure 4). The complex I activity was decreased in ERVWE1-overexpressing cells compared to that in control cells ($P < 0.05$; Figure 6A).

We measured complex I activity after the knockdown of NDUFV2P1 in SH-SY5Y cells. Downregulating NDUFV2P1 could mitigate ERVWE1-induced inhibition of mitochondrial complex I in SH-SY5Y cells ($P < 0.05$; Figure 6B), indicating that ERVWE1 inhibited complex I activity by increasing NDUFV2P1.

Another experiment showed that CPEB1 could reverse the complex I deficiency induced by ERVWE1 in SH-SY5Y cells ($P < 0.05$; Figure 6C), suggesting that ERVWE1 could regulate complex I activity *via* suppressing CPEB1 expression.

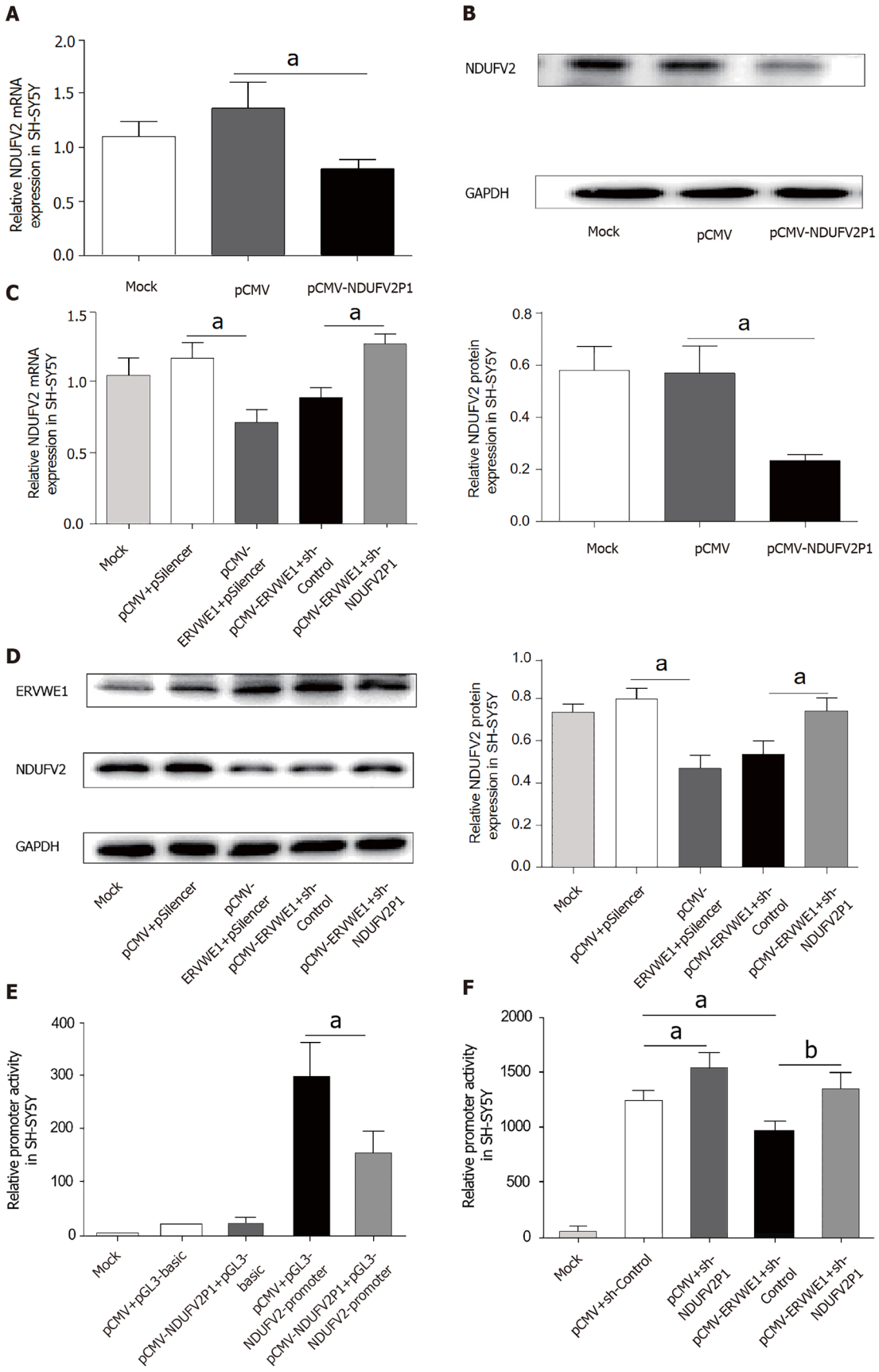


Figure 3 Role of NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) pseudogene (NDUFV2P1) in ERVWE1-induced downregulation of NDUFV2. A: The mRNA levels of NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) in NDUFV2 pseudogene (NDUFV2P1)-overexpressing SH-SY5Y cells using quantitative polymerase chain reaction (qPCR); B: Western blots of NDUFV2 and GAPDH in SH-SY5Y cells; C: The mRNA levels of NDUFV2 in SH-SY5Y cells after co-transfection with ERVWE1 and shNDUFV2P1 using qPCR; D: Western blots of ERVWE1, NDUFV2, and GAPDH in SH-SY5Y cells; E: Luciferase assays of pGL3-NDUFV2 promoter co-transfected with pCMV-NDUFV2P1 or control vector in SH-SY5Y cells; F: Luciferase assays of

pGL3-NDUFV2 promoter co-transfected with pCMV-ERVWE1 + shNDUFV2P1 or control in SH-SY5Y cells. Each bar represents the mean ± SD of three independent experiments. $^{a}P < 0.05$; $^{b}P < 0.01$.

In summary, our data indicate that ERVWE1 modulates mitochondrial energy metabolism, primarily of complex I, *via* the CPEB1/NDUFV2P1/NDUFV2 signaling pathway in schizophrenia.

DISCUSSION

Schizophrenia is a multifactorial mental disorder with abnormal cognitive functions and behavior. It is characterized by continuous or relapsing episodes of psychosis. Potential blood-based biomarkers have the potential to increase the precision of the diagnostic and prognostic process for schizophrenia. The field of blood-biomarker discovery for schizophrenia is coming to fruition as patient blood is an easily accessible biological sample[29]. An increasing number of molecular detection techniques with high specificity and sensitivity are currently applied in the search for serum markers or genetic markers in peripheral blood. Previous studies have addressed potential blood-based biomarkers for schizophrenia, such as microRNA[30, 31], insulin-related peptides[32,33], and inflammatory cytokines[34]. However, no biomarkers have been successfully used in the clinical diagnosis of schizophrenia. GWAS has implicated CPEB1, which possesses a highly conserved RNA-binding domain and controls the cytoplasmic polyadenylation of mRNA by combining with the specific sequences, as a novel schizophrenia susceptibility gene[27,35]. However, there is no experimental evidence of an association between CPEB1 and schizophrenia. Clinical data of this study do not follow a normal distribution, so Spearman's rank correlation was used for correlation analyses. In this paper, clinical data showed that CPEB1 was decreased and negatively correlated with ERVWE1 in schizophrenia. Univariate and multivariate analyses suggested that CPEB1 might be a novel potential blood-based biomarker and risk factor for schizophrenia.

The mouse model has shown that knockout of CPEB1 downregulates NDUFV2 protein expression[16]. The abnormal expression of NDUFV2 has been found in schizophrenia[7,36]. Our data displayed decreased NDUFV2 transcription in schizophrenia, in contrast to the data reported by Haghighatfard *et al*[36]. The reason for this might be the primer used by Haghighatfard's group can detect not only NDUFV2 but also NDUFV2P1. Herein, our primers could successfully detect the transcript levels of NDUFV2 and NDUFV2P1. The NDUFV2P1 transcript was upregulated in schizophrenia and was negatively regulated NDUFV2. Additionally, our previous study showed false positives using nonspecific primers to detect both NDUFV2 and NDUFV2P1 (Supplementary Figure 5). We also found decreased NDUFV2 protein expression, consistent with the report by Bergman *et al*[14]. However, Bergman *et al* [14] showed no changes in NDUFV2 mRNA. The primary factor driving the difference between our and Bergman's findings is that we focused on recent-onset schizophrenia patients. In our sample, all subjects with recent-onset schizophrenia were free from antipsychotics, whereas in the schizophrenia samples of Bergman's group, all but one participant were using antipsychotic medications. A previous study demonstrated that exposure to antipsychotic medication can increase NDUFV2 mRNA expression in Sprague-Dawley rats[37]. Hence, antipsychotic medication treatment might reverse the downward trend of NDUFV2 and result in no change at the mRNA level. NDUFV2P1 is a non-transcribed pseudogene of NDUFV2. There are few studies on NDUFV2P1. Only one study has reported that schizophrenia-derived cells have increased expression of NDUFV2P1[14]. Similarly, we found that NDUFV2P1 was significantly increased and negatively correlated with NDUFV2 in schizophrenia patients. ERVWE1 is associated with schizophrenia[18]. Further analyses indicated that ERVWE1 was negatively correlated with NDUFV2 and positively correlated with NDUFV2P1 in schizophrenia patients.

The etiology of schizophrenia remains unclear. Scientists believe that both environmental and genetic factors contribute to the risk of schizophrenia. Several studies have indicated that ERVWE1, a new pathogenic factor in schizophrenia, acts as a bridge and trigger between environmental and genetic factors. A series of environmental factors may activate the ERVWE1, a protein displaying inflammation and neurotoxicity[38]. Several studies have shown that ERVWE1 mediates neuroinflammation *via* the Toll-like receptor pathway in schizophrenia[19,38,39] or multiple sclerosis (MS)[40].

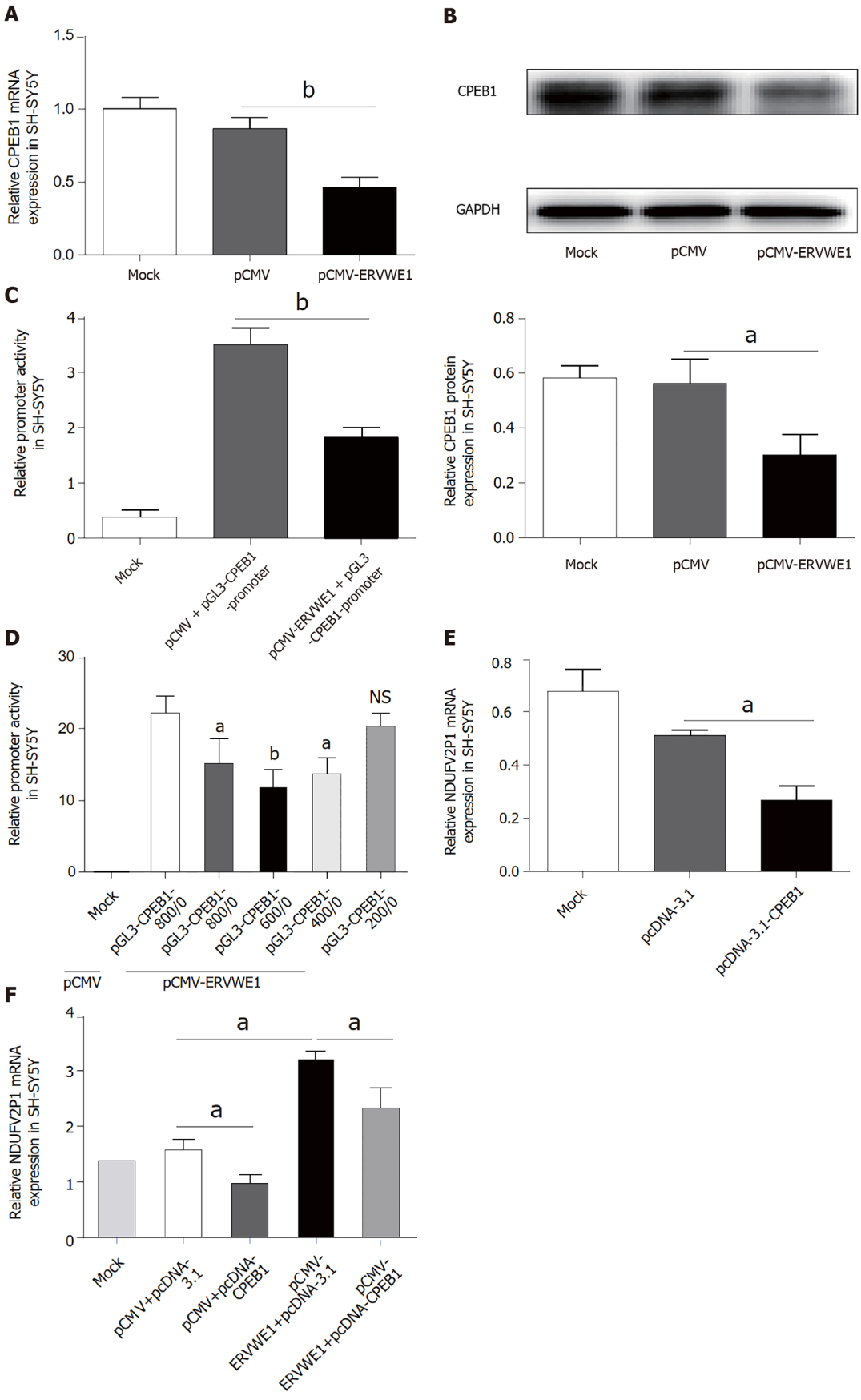


Figure 4 ERVWE1 elevated NADH dehydrogenase ubiquinone flavoprotein 2 pseudogene (NDUFV2P1) expression by suppressing cytoplasmic polyadenylation element-binding protein 1 (CPEB1). A: The mRNA levels of cytoplasmic polyadenylation element-binding protein 1 (CPEB1) after overexpression of ERVWE1 in SH-SY5Y cells using quantitative polymerase chain reaction (qPCR); B: Western blots of CPEB1 and GAPDH in SH-SY5Y cells; C: Luciferase assays of pGL3-CPEB1 promoter co-transfected with pCMV-ERVWE1 or control vector in SH-SY5Y cells; D: Luciferase assays of different

lengths of pGL3-CPEB1 promoter co-transfected with pCMV-ERVWE1 or control vector in SH-SY5Y cells; E: The mRNA levels of NADH dehydrogenase ubiquinone flavoprotein 2 pseudogene (NDUFV2P1) after overexpression of CPEB1 in SH-SY5Y cells using qPCR; F: Represent the mRNA levels of NDUFV2P1 in SH-SY5Y cells after co-transfection with ERVWE1 and CPEB1 using qPCR. Each bar represents the mean ± SD of three independent experiments. $^{a}P < 0.05$; $^{b}P < 0.01$; NS: Not significant.

Moreover, ERVWE1 can activate inducible nitric oxide synthase activity and induce cytotoxic T lymphocyte responses[38]. Further studies on the delineation of a role for retroviruses in schizophrenia will bring new diagnosis and treatment of the devastating schizophrenia.

NDUFV2P1 is a potential predictive marker in schizophrenia by negatively regulating its parent gene, NDUFV2[14]. Based on the findings that ERVWE1 can regulate some schizophrenia-related genes[18,38], we conducted additional studies to examine the potential relationship among ERVWE1, NDUFV2P1, and NDUFV2 in schizophrenia. Previous research suggests that ERVWE1 is overexpressed in brain tissues[41]. To study the possible role of ERVWE1, we selected the SH-SY5Y cell line, a human-derived neuroblastoma cell with neuronal function and differentiation and widely used as *in vitro* model for neuronal studies. Our results indicated that ERVWE1 induced upregulation of NDUFV2P1 and downregulation of NDUFV2. Pseudogenes exhibit essential roles in gene expression and gene regulation. They are capable of regulating parental genes or act as a competitive endogenous RNA (ceRNA)[28] or small interfering RNA[42]. Our results showed that NDUFV2P1 acted as a ceRNA in NDUFV2 expression induced by ERVWE1.

The NDUFV2 promoter plays essential roles in its expression[11]. ERVWE1 has been proposed to regulate the activation of promoters and control the expression of some schizophrenia-related genes[18,19]. We found that NDUFV2P1 participated in the process of ERVWE1 suppressing the NDUFV2 promoter. It has been suggested that NDUFV2P1 possibly competes with NDUFV2 by interfering with its mRNA[43]. Retrocopies or processed pseudogenes, the majority of the human pseudogenes, are gene copies originating from mRNA retrotransposition. Our observation might reveal another way of regulating parental genes by their retrocopies. From these, we could conclude that ERVWE1 inhibited the NDUFV2 promoter by raising the NDUFV2P1 transcript.

Schizophrenia is linked to mitochondrial energy metabolism dysfunction. CPEB1 controls polyadenylation-induced translation of NDUFV2 mRNA and results in impaired brain-specific mitochondrial respiration[16]. In this work, we found that ERVWE1 dramatically lowered CPEB1 levels *via* inhibiting its promoter and that the range of -400 to 0 was necessary. We found a new regulatory mechanism that is different from the conserved mechanism of CPEB1. Interestingly, overexpression of CPEB1 led to increased protein levels of NDUFV2 with no change at the transcript level. The data are in line with another study[16]. Furthermore, CPEB1 reduced the NDUFV2P1 transcript. To date, there have been no published data on the mechanisms that regulate NDUFV2P1. Our finding might be the first report of NDUFV2P1 regulation in schizophrenia. Further studies are needed to determine precisely how CPEB1 affects pseudogene transcripts. Moreover, overexpression of CPEB1 decreased the NDUFV2P1 levels induced by ERVWE1. Simultaneously, overexpression of CPEB1 substantially elevated the expression of NDUFV2 inhibited by ERVWE1. Our results suggested that ERVWE1 regulated NDUFV2P1/NDUFV2 signaling pathway through the suppression of CPEB1.

Ample evidence indicates that impaired mitochondrial energy metabolism may be compromised in schizophrenia patients[44,45]. Complex I deficiency is among the most encountered defects of mitochondrial energy metabolism[46]. Complex I, also names NADH:ubiquinone oxidoreductase, is the largest and the most elaborate component of the mitochondrial respiratory chain. It catalyzes the oxidation of NADH, together with the transfers of two electrons to the ubiquinone. Complex I deficiency is associated with abnormalities in calcium signaling[46,47]. The possible role of calcium signaling in schizophrenia is initially presented by Jimerson *et al*[48]. Our previous report demonstrated that ERVWE1 can induce calcium influx in human neuroblastoma cells[49]. Therefore, we speculated that ERVWE1 might cause the decrease of complex I activity in schizophrenia. Herein, we found overexpression of ERVWE1 suppressed complex I activity. Knockdown of NDUFV2P1 significantly restored the complex I activity suppressed by ERVWE1. This observation suggested that NDUFV2P1 was required in the ERVWE1-induced complex I activity deficiency. CPEB1 is essential to promote mitochondrial energy production in neurons[15]. CPEB1 knockdown cells have reduced complex I activity and mitochondria number[16,50].

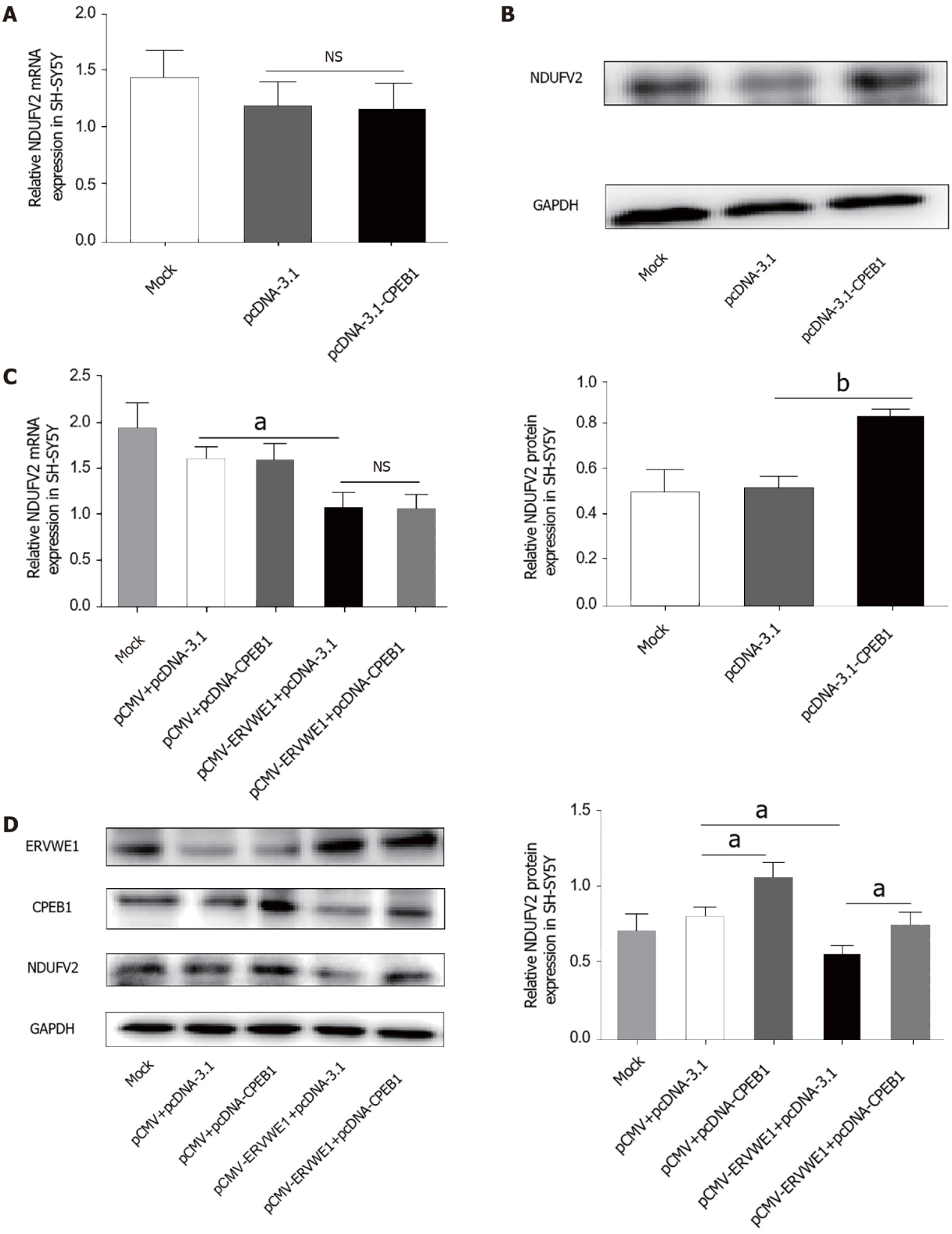


Figure 5 ERVWE1 reduced NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) expression by suppressing cytoplasmic polyadenylation element-binding protein 1 (CPEB1). A: The mRNA levels of NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) after overexpression of cytoplasmic polyadenylation element-binding protein 1 (CPEB1) in SH-SY5Y cells using quantitative polymerase chain reaction (qPCR); B: Western blots of NDUFV2 and GAPDH in SH-SY5Y cells; C: Represent the mRNA levels of NDUFV2 in SH-SY5Y cells after co-transfection with ERVWE1 and CPEB1 using qPCR; D: Western blots of ERVWE1, CPEB1, NDUFV2, and GAPDH in SH-SY5Y cells. Each bar represents the mean ± SD of three independent experiments. $^{a}P < 0.05$; $^{b}P < 0.01$; NS: Not significant.

Our results showed that CPEB1 overexpression could rescue complex I activity, which was inhibited by ERVWE1. As a core subunit of this complex, NDUFV2 is a crucial regulator of complex I activity, depletion and phosphorylation of this protein causes a decrease in complex I activity[51,52].

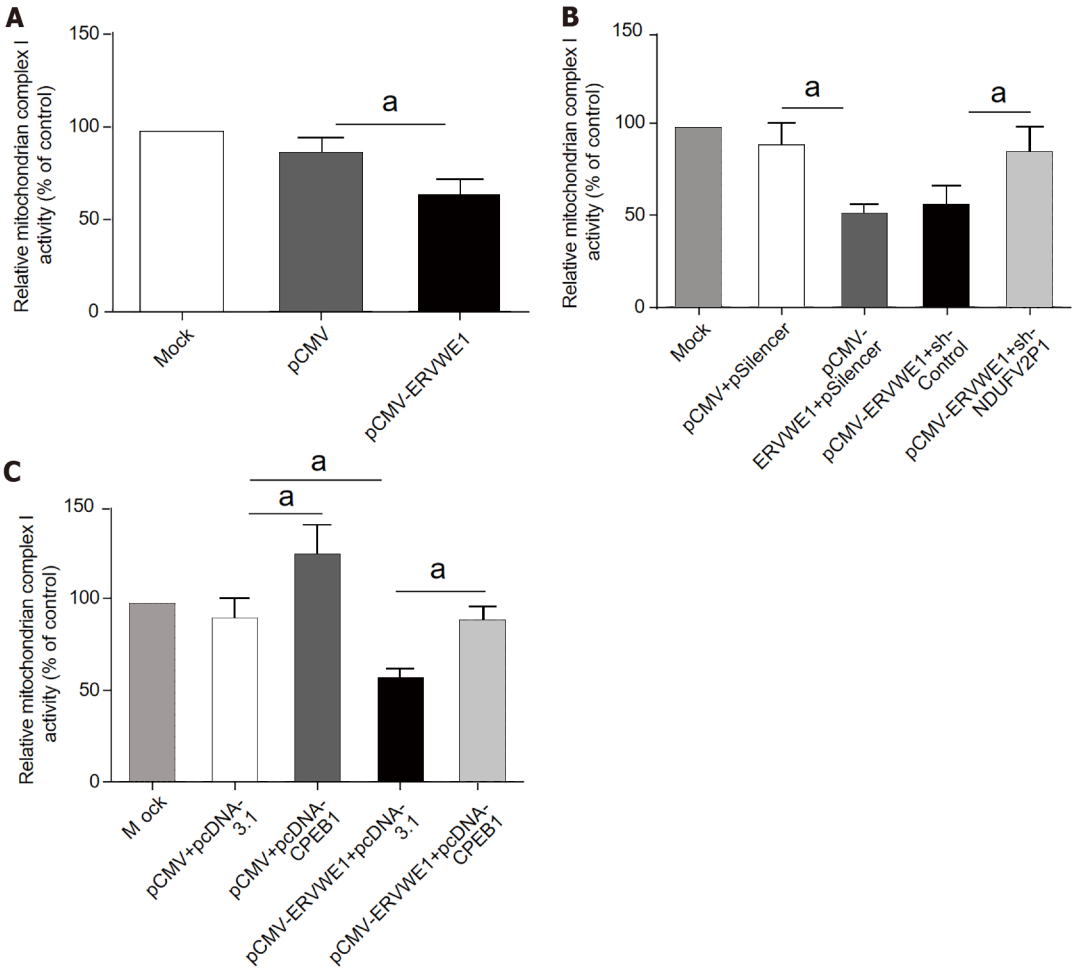


Figure 6 ERVWE1 contributed to complex I deficits through the cytoplasmic polyadenylation element-binding protein 1 (CPEB1)/ NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) pseudogene (NDUFV2P1)/NDUFV2 signaling pathway. A: Complex I activity in SH-SY5Y cells transfected with pCMV-ERVWE1 or control; B: Complex I activity in SH-SY5Y cells co-transfected with pCMV-ERVWE1 + shNDUFV2P1 or control; C: Complex I activity in SH-SY5Y cells co-transfected with pCMV-ERVWE1 + pcDNA3.1-CPEB1 or control. Each bar represents the mean ± SD of three independent experiments. $^{a}P < 0.05$.

Schizophrenia mostly sets in after the age of 20. Mitochondrial energy metabolism dysfunction has been implicated in the etiology of schizophrenia in early adulthood from age 20-30[53]. Research from our and others suggests that environmental factors, including viral infection, drug stimulation, and genetic variation, can cause abnormal expression of ERVWE1. In this study, we demonstrated that increased ERVWE1 induces mitochondrial metabolism deficits, which ultimately leads to the pathogenesis of schizophrenia. In summary, ERVWE1 overexpression contributes to complex I deficits in schizophrenia *via* the CPEB1/NDUFV2P1/NDUFV2 signaling pathway.

CONCLUSION

In conclusion, the purpose of this study was to discover novel potential blood-based biomarkers and reveal the potential mechanisms underlying ERVWE1-mediated mitochondrial energy metabolism defects in schizophrenia. We reported that the expression of CPEB1 was lower and negatively correlated with ERVWE1 in schizophrenia blood samples. This study is to identify CPEB1 as a novel potential blood-based biomarker for schizophrenia. We also found that NDUFV2 exerted an inverse expression with NDUFV2P1 and ERVWE1 in schizophrenia. Further analyses showed a positive correlation and marked consistency between expressions of NDUFV2P1 and ERVWE1. *In vitro* experiments demonstrated that ERVWE1 mediated the downregulation of NDUFV2 by upregulating its pseudogene, NDUFV2P1. Moreover, CPEB1 was decreased after ERVWE1 overexpression and worked as a mediator of the NDUFV2P1/NDUFV2 signaling pathway induced by ERVWE1. Further studies

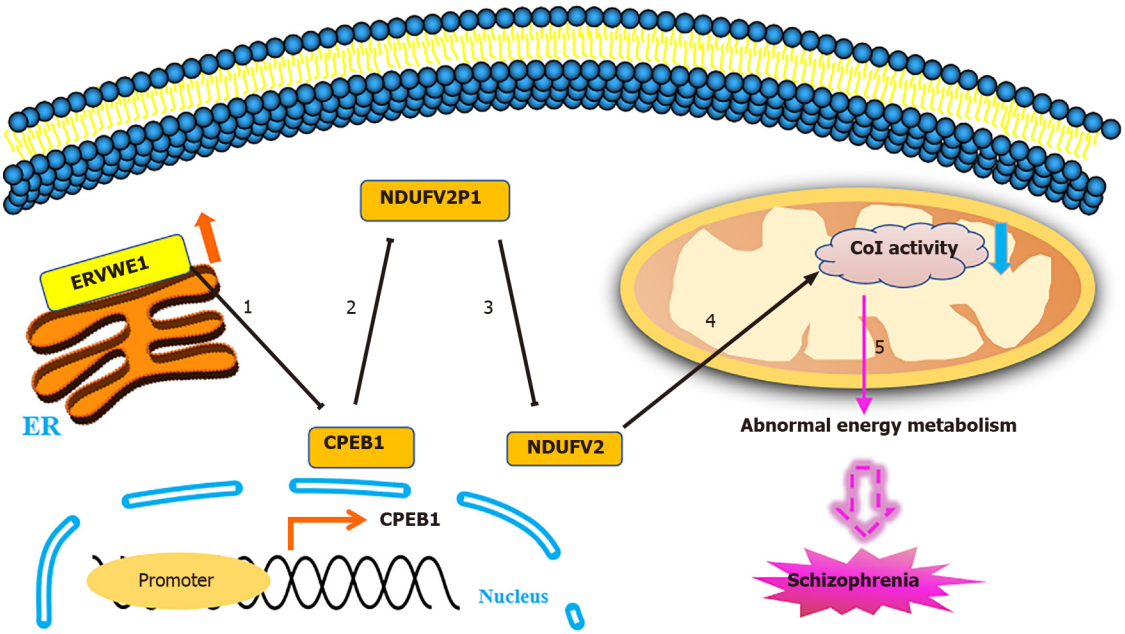


Figure 7 The proposed signaling pathways for ERVWE1 contributes to mitochondrial energy metabolism deficiency in schizophrenia. 1: ERVWE1 suppressed cytoplasmic polyadenylation element-binding protein 1 (CPEB1) mRNA and protein expression by regulating its promoter activity; 2: ERVWE1 upregulated the expression of NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2) pseudogene (NDUFV2P1) through enhancing its promoter activity. CPEB1 downregulated NDUFV2P1 expression and functioned as a mediator of NDUFV2P1 transcript induced by ERVWE1; 3: NDUFV2P1 reduced NDUFV2 expression through inhibiting its promoter activation. Additionally, ERVWE1 decreased the mRNA and protein expression of NDUFV2 and suppressed NDUFV2 promoter through increasing NDUFV2P1 transcript. Moreover, CPEB1 was involved in regulating NDUFV2P1/NDUFV2 signaling pathway triggered by ERVWE1; 4: ERVWE1 reduced complex I activity *via* regulating NDUFV2 and its retrocopies expression. Decreased CPEB1 was involved in the complex I activity deficiency induced by ERVWE1; 5: Deficient complex I activity might result in mitochondrial metabolic dysregulation and contributed to the development of schizophrenia.

indicated that ERVWE1 impaired mitochondrial complex I activity, which might lead to mitochondrial metabolic dysregulation through the CPEB1/NDUFV21P1/NDUFV2 signaling pathway (Figure 7). As a novel potential blood-based biomarker and risk factor, further studies and clinical research are needed better to understand the role of decreased CPEB1 and NDUFV2 in schizophrenia to develop this paradigm into an effective treatment strategy.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia is a devastating psychiatric disorder that impairs mental and social functioning. There are several hypotheses regarding the pathogenesis of schizophrenia, including mitochondrial dysfunction. Both genetic and environmental factors contribute to the development of schizophrenia. Our previous studies showed that ERVWE1 acts as a bridge between genetic and environmental factors and plays an important role in the occurrence of schizophrenia.

Research motivation

Schizophrenia is a chronic disorder requiring long-term treatment and having a significant impact on patients and their families. Biomarkers and pathogenic mechanisms have become the most important undertaking for schizophrenia. In this manuscript, we focused on the relationship between mitochondrial energy metabolic deficits and ERVWE1 in schizophrenia.

Research objectives

This study aimed to identify novel potential blood-based biomarkers and risk factors for schizophrenia and to explore the underlying mechanisms ERVWE1-mediated mitochondrial metabolic deficits in schizophrenia.

Research methods

Quantitative polymerase chain reaction (qPCR) and enzyme-linked immunosorbent assay were used to detect differentially risk genes expression in blood samples. Statistical analyses of clinical data were performed by median analysis, Mann-Whitney U analysis, and Spearman's rank correlation analysis. qPCR, western blotting, luciferase assay, and complex I enzyme activity microplate assay were performed to study the relationship between ERVWE1, CPEB1, NADH dehydrogenase ubiquinone flavoprotein 2 (NDUFV2), and NDUFV2 pseudogene (NDUFV2P1).

Research results

CPEB1 and NDUFV2 were deceased and negatively correlated with ERVWE1 in schizophrenia. Moreover, Increased NDUFV2P1 demonstrated a significant positive correlation with ERVWE1 and negative correlation with NDUFV2 in schizophrenia. Cytological experiments demonstrated that ERVWE1 suppressed CPEB1 by suppressing its promoter activity and downregulated NDUFV2 expression through increasing NDUFV2P1 transcript. Further studies showed that CPEB1 participated in regulating the NDUFV2P1/NDUFV2 axis mediated by ERVWE1 in SH-SY5Y cells. Finally, we found that ERVWE1 regulated complex I activity through the CPEB1/NDUFV2P1/NDUFV2 signaling pathway in SH-SY5Y cells.

Research conclusions

CPEB1 and NDUFV2 were identified as novel risk factors in schizophrenia. We also proposed a novel mechanism that ERVWE1 mediated mitochondria metabolic deficits through the CPEB1/NDUFV2P1/NDUFV2 signaling pathway in schizophrenia.

Research perspectives

Further study is needed to verify if CPEB1 and NDUFV2 can be used as blood-based biomarker of schizophrenia. As a risk factor, further efforts need to be focused on better understand the role of ERVWE1, CPEB1 and NDUFV2 in the pathogenesis of schizophrenia. Although our study suggests that ERVWE1 may be a potential therapeutic target for schizophrenia, whether ERVWE1 can really benefit clinical treatment requires further research in animal experiments and clinical trials to confirm these data.

ACKNOWLEDGEMENTS

We thank Wang Y (Master of Science in Epidemiology and Biostatistics) for assistance with the biostatistical analyses.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 1095-1105

DOI: 10.5498/wjp.v11.i11.1095

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Psychiatric hospitalization during the two SARS-CoV-2 pandemic waves: New warnings for acute psychotic episodes and suicidal behaviors

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Author contributions: Panariello F analyzed the data, managed the literature searches and analyses, and wrote the first draft of the manuscript; Fabio P, Longobardi S, and Cellini L wrote the protocol and collected the data; De Ronchi D designed the study and amended the last draft of the manuscript; Atti AR designed the study, improved the first draft of the manuscript, and conducted the statistical analyses; All authors managed the literature searches and helped Panariello F write the manuscript and approved the final manuscript.

Institutional review board statement: This study has been conducted in agreement with our Institutional Guidelines.

Informed consent statement: The informed consent statement was waived.

Conflict-of-interest statement: All authors declare that they have no

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Abstract

BACKGROUND

The subsequent waves of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic have represented a dramatic health emergency characterized by significant consequences on mental health. Diachronic variations in the incidence rates of acute relapse of psychiatric disorders may represent significant "sentinel events" for assessing the mental health response to an unprecedented stressful event.

AIM

To investigate the variation in psychiatric hospitalization rates and differences in sociodemographic and clinical-psychopathological peculiarities at Bologna "Maggiore" General Hospital Psychiatric Ward (GHPW) between the first two waves SARS-CoV-2 pandemic and the same periods of the previous 3 years. The secondary purpose of the study was to suggest a diachronic response pathway to stress by reporting additional literature data on coping strategies.

METHODS

This observational and retrospective study collected information on admission to the GHPW at the "Maggiore" Hospital in Bologna in the index periods defined as follows: the first period between February 24, 2020 and April 30, 2020 (first epidemic wave) and the second period between October 8, 2020, and January 7, 2021 (second pandemic wave). Absolute numbers and proportion of admitted patients, their sociodemographic and clinical-psychopathological characteristics were compared with the same parameters recorded in the two same periods of the previous 3 years. No strict inclusion or exclusion criteria were provided in the data collection to collect information on all patients requiring acute psychiatric

conflicts of interest to declare.

Data sharing statement: No additional data are available.

Country/Territory of origin: Italy

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: April 30, 2021
Peer-review started: April 30, 2021
First decision: July 14, 2021
Revised: July 23, 2021
Accepted: September 3, 2021
Article in press: September 3, 2021
Published online: November 19, 2021

P-Reviewer: Sergi CM
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Liu JH

hospitalization.

RESULTS
During the first wave, there was a significant reduction in hospitalization rates, although there was a simultaneous increase in compulsory hospitalizations and the acute relapse of schizophrenia spectrum and other psychotic disorders. During the second wave, hospitalization rates reached those recorded during the same period of the previous 3 years, mainly due to the rise of bipolar and related disorders, depressive disorders, anxiety disorders, trauma- and stressor-related disorders and suicidal behaviors.

CONCLUSION
The coping strategies adopted during the first wave of the SARS-CoV-2 pandemic protected the vulnerable population from the general risk of clinical-psychopathological acute relapse, even if they increased the susceptibility to run into schizophrenia spectrum and other psychotic disorder relapses. In the medium-long term (as in the second pandemic wave), the same strategies do not play protective roles against the stress associated with the pandemic and social restriction measures. Indeed, during the second wave of the SARS-CoV-2 pandemic, an increase in total hospitalization rate, suicidal behaviors and the incidence rate of bipolar and related disorders, depressive disorders, anxiety disorders, trauma- and stressor-related disorders was observed.

Key Words: SARS-CoV-2; Schizophrenia spectrum and other psychotic disorders; Bipolar and related disorders; Depressive disorders; Anxiety disorders, trauma- and stressor-related disorders; Suicide behavior; Coping strategies

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Core Tip: The severe acute respiratory syndrome coronavirus 2 emergency has impacted global health. This study describes psychiatric hospitalization rates and clinical characteristics during changes in the first two epidemic waves compared to the respective periods of the previous 3 years. Although the hospitalization rate decreased during the first pandemic wave, compulsory hospitalizations have increased. During the second pandemic wave, hospitalization rates returned to those recorded in the same period of the previous 3 years. Acute relapse in psychotic disorders increased during the first epidemic wave, but acute relapse in affective and anxiety disorders have increased in the second epidemic wave as well as suicidal behavior.

Citation: Panariello F, Longobardi S, Cellini L, De Ronchi D, Atti AR. Psychiatric hospitalization during the two SARS-CoV-2 pandemic waves: New warnings for acute psychotic episodes and suicidal behaviors. *World J Psychiatr* 2021; 11(11): 1095-1105
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1095.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1095

INTRODUCTION

In Italy, the first epidemic outbreak occurred at the end of February 2020 in Lombardy [1]. The Italian government adopted several social distancing measures and limitations of social recreational and work activities at national and regional levels to contain infection spread. These measures progressively increased until the lockdown imposed by the Prime Minister's Decree of Ministers of March 9, 2020. Similarly, from the first decade of October 2020, in order to contain the spread of the second pandemic wave, the Italian Prime Minister issued another set of social distancing measures up to a level of limitation similar to the first lockdown. Details on social distancing measures during the first and second waves in Italy are reported in Table 1.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related pandemic threatened the health of citizens and significantly contributed to a widespread sense of insecurity and a lessened quality of life for both individuals and

Table 1 First and second pandemic waves and social distancing measures

First wave (February 24, 2020 to April 30, 2020), 66 d	Second wave (October 8, 2020 to January 7, 2021), 92 d
Main governative measures	**Main governative measures**
Smart working (more than 50%)	Smart working (8%-40%)
Distance learning (more than 75%)	Distance learning (75%-100%)
In and outdoor mask wearing (always)	In and outdoor mask wearing
Leisure activities limitations	Leisure activities limitations
Relatives and friends restricted visiting	Relatives and friends restricted visiting
Travelling limitations	Travelling limitations
Cinemas, theaters, museums, betting halls closure	Cinemas, theaters, museums, betting halls closure
Bars and restaurants closure from total closure to closure from 6.00 pm (prohibited on-site consummation)	Bars and restaurant closure from 6.00 pm (prohibited on-site consummation)
Night curfew (from 8:00 pm)	Night curfew (from 9:00 pm)

entire communities[2]. Such psychosocial effects on individuals (*e.g.*, insecurity, fear, uncertainty, confusion, isolation, and stigma) and the whole community (*e.g.*, school and workplace closures, the shutdown of social gathering places, suspension of economic activities, and uncertainty in health claims) may have contributed to threatening the mental health of individuals and the collective[3,4] and causing both new onsets of clinical pictures from adjustment disorders and relapses of psychiatric disorders from severe mental illness (SMI)[5-7]. These consequences have already been reported in the general population[8,9], vulnerable individuals[7,10], and patients with a history of psychiatric disorders[11]. Furthermore, the long-term consequences on mental health are likely to continue even after the end of the pandemic emergency, resulting, for example, from the economic burden due to the adopted social distancing measures. In epidemiological terms, it could be worse than the consequences on the mental health during the economic crisis in Italy and Greece in 2008, where a significant increase of suicidal behaviors and suicide occurred, as was well described in the literature[12,13].

The Italian mental health system is extensively community-based, and mental health care is freely available to all citizens. Besides outpatient settings, in Italy, there are nearly 318 psychiatric wards located within the general hospitals (General Hospital Psychiatric Wards [GHPWs]). Each ward contains, on average, 15 beds dedicated to treating psychiatric patients in both voluntary and compulsory ways[14]. The total national number of beds to take care of acute psychiatric clinical pictures is 3981, which means around 10 beds *per* 100000 adult population[14]. Therefore, GHPWs are places of care dedicated to the hospitalization and treatment of acute psychopathological relapses that can be configured as psychiatric emergencies/urgencies. They represent a privileged observatory to survey the changes, in terms of incidence, of new-onset or acute relapse of clinical pictures related to SMIs such as those observed during the exposure to high-stress life events. For this reason, they play a crucial role during global crises that also involve mental health and represent a fundamental source of information to be collected in the early stages of a crisis, valuable both to better understand individual and collective coping strategies and to implement preventive actions and timely care[15-17].

Only a few studies[16,18] have examined and described qualitative and quantitative differences observed in the rates of urgent/emergent hospitalization within the psychiatric wards between the pre-pandemic and SARS-CoV-2 pandemic characterized by the consistent social restriction measures. Furthermore, to the best of our knowledge, no studies to date have investigated these differences during the first and second pandemic waves.

This study investigated the existence of any differences in terms of acute psychiatric relapse or new onset of psychiatric disorders observed at the GHPW of the "Maggiore" Hospital in Bologna between the first and second epidemic wave compared to the same periods of the previous 3 years by comparing the sociodemographic and clinical features.

To achieve this aim, we took into consideration: Voluntary hospitalization rates, compulsory hospitalization rates, diagnoses, and the severity of psychopathological-clinical pictures estimated by the mental health triage (MHTS)[19,20].

Furthermore, based on our results and the collection of scientific evidence that we have collected in the literature regarding the response of individuals and communities to stressful factors and their persistence over time, we propose an opinion review to depict a hypothetical model of the diachronic response of the community to unusually stressful and unprecedented events. We hypothesize that the coping strategies and their efficacy can change over time and, depending on the individual aptitude to answer to the stress, we have generated an "elastic" model that can give reason to the different psychopathological pictures observed over time, after and during a stressful event.

MATERIALS AND METHODS

Participants

This observational and retrospective study collected information on admissions to the GHPW at the "Maggiore" Hospital in Bologna in the index periods defined as follows: the first period between February 24, 2020 and April 30, 2020 (first epidemic wave) and the second period between October 8, 2020, and January 7, 2021 (second pandemic wave). Absolute numbers and the proportion of admitted patients, their sociodemographic and clinical-psychopathological characteristics were compared with the same parameters recorded in the two same periods of the previous 3 years. No strict inclusion or exclusion criteria were provided in the data collection to collect information on all patients requiring acute psychiatric hospitalization. This study followed the last version of the Declaration of Helsinki[21].

Assessment

For each patient hospitalized in the index periods, clinical data were collected, determining the diagnosis and the level of emergency/urgency at the time of admission based on the MHTS by the Victorian Emergency Department[19,20]. The MHTS is a triage scale aimed at identifying the severity level of psychopathological pictures to prioritize the intervention. It consists of a five-level scale: Level 1, the substantial danger of life to oneself and others; Level 2, violent, aggressive, probable danger of injury to oneself or others or with police escort; Level 3, very distressed or psychotic, liable to deteriorate, situational crisis, possible danger to oneself or others; Level 4, long-lasting semi-urgent mental health disorder, support agency present; and Level 5, long-standing non-acute mental health disorder, no support agency present. Patients were assessed using combined mental health and sociodemographic information.

Hospitalized patients were divided into emergent (Level 1 and 2) and urgent (Level 3, 4, and 5) cases. In the hospitalized population, the incidence rate of compulsory hospitalizations was calculated [according to the Italian law (Law number 180/1978), in case of acute psychopathological distress, when patients lack insight and refuse the treatments which they need, and there are no possibilities to provide outpatient treatments, psychiatric admissions against the patient's will are possible - compulsory admissions[22]. We also collected other data such as sociodemographic data (sex, age) and the length of hospitalization. Age was used as a continuous variable. Diagnoses were assessed according to the DSM 5 through the administration of the Structured Clinical Interview for the DSM 5 Clinician Version (SCID-5-CV). The SCID-5-CV is characterized by excellent reliability and high specificity, and there is evidence for its easy use in daily clinical practice[23].

Statistical analyses

Continuous data for sociodemographic and clinical variables are expressed as the mean ± SD, while categorical variables are reported as percentages. The Kolmogorov-Smirnov test was performed to verify normal distributions of continuous variables. Multiple logistic regression analyses were performed by including variables that were significant for bivariate analysis. Pearson's chi-squared test with Yates correction or the *t*-test for independent samples was used to compare categorical and continuous variables, respectively, between the identified subgroups. As the dependent variable, we used GHPW hospitalization during the pandemic. Odds ratio (OR) and 95% confidence interval (95%CI) were calculated to estimate the correlation between the frequencies of the hospitalization and the frequencies of independent variables. All statistical analyses were performed using the SPSS package (version 27.0, SPSS; SPSS Inc., Chicago, IL, United States) for Windows, and $P < 0.05$ (two-tailed) was considered statistically significant.

RESULTS

During the first index period, we observed 47 inpatients at GHPW "Maggiore" Hospital in Bologna (84 hospitalized patients during the second index period); 42.58% of the hospitalized population was female (*vs* 43.2% during the second lockdown). The mean age was 42 + 2 (years + SD) during the first index period (*vs* 43.9 + 1 during the second index period). The length of hospitalization was 8.8 + 3 d in the first index period and 8.5 + 2 d in the second index period. According to MHTS, 85.7% of the admitted patients were classified as urgency during the first index period (80.7% during the second index period). No differences were observed between the two pandemic waves and the same periods of the previous 3 years in length of hospitalization, mean age, and sex.

A reduction in total psychiatric hospitalization number during the first lockdown of 33.49% compared to the hospitalization rate in the same period of the previous 3 years was reported (47 in 2020 *vs* 81 in 2019, 68 in 2018, and 63 in 2017 for further details; Table 2). On the other hand, an increase in compulsory admissions was observed: 19.7% of total admissions that occurred during the first lockdown compared to 10.1% ($P < 0.01$) in the same period of 2019, 13.3% ($P < 0.05$) in 2018, and 7.2% in 2017 ($P < 0.01$). Consistently with these features, hospitalized patients presented a higher degree of psychopathological emergency at MHTS than in the same period of the previous 3 years (28.2% *vs* 13.6% [$P < 0.01$] in 2019, 25% [$P < 0.05$] in 2018, and 14.3% in 2017 [$P < 0.01$]) (Table 2).

During the first pandemic wave and related restriction measures, schizophrenia spectrum and other psychotic disorders diagnoses increased by 10% on average. As indicated in Table 2, 39.5% in 2020 *vs* 32.1% in 2019 ($P < 0.05$), 31.5% in 2018 ($P < 0.05$), 25.1% in 2017 ($P < 0.01$). Anxiety disorders and trauma- and stressor-related disorders (Group C in Table 2) showed an increasing trend during the first lockdown (8% in 2020 *vs* 5.2% in 2019, 5.9% in 2018, and 5.8% in 2017). Logistic regression analyses considering hospitalization at GHPW during the first pandemic wave and the estimated probability ratio (OR) was as follows: Male/female (OR = 1.754; $P < 0.001$), self-harm behavior (OR = 2.066; $P < 0.001$) as an independent variable (Table 3). During the second wave, hospitalization numbers increased reaching the same rate recorded during the previous 3 years (84 *vs* 89 in 2019, 85 in 2018, 88 in 2017) while the proportion of compulsory admissions and the level of emergency, according to the MHT, decreased to the percentages observed in the same period of the previous 3 years (Table 4).

Bipolar and related disorders, depressive disorders, anxiety disorders, and trauma- and stressor-related disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM5) were those that were statistically increased significantly during the second pandemic wave compared to the same period of the three previous years. Bipolar and related disorders and depressive disorders were 32.9% of total hospitalizations *vs* 28.8% ($P < 0.01$) in 2019, 29.4% ($P < 0.05$) in 2018, 30.1% ($P < 0.05$) in 2017, in the same period of the previous 3 years. The disorders belonging to anxiety disorders and trauma- and stressor-related disorders according to the DSM5 during the second pandemic wave and related restrictive measures were 9% of total hospitalizations *vs* 4.2% ($P < 0.01$) in 2019, 3.7% ($P < 0.01$) in 2018 and 2.1% ($P < 0.01$) in 2017. We also observed a statistically significant increase in suicidal behavior during the second pandemic wave compared with the average recorded during the same period of the previous 3 years (20.22% *vs* 11.10%; $P < 0.01$). Disorders belonging to the schizophrenia spectrum were more prevalent in the second pandemic wave (10.4%) than in the same period of the previous 3 years, albeit not statistically significant. Logistic regression analyses considering hospitalization at GHPW during the second pandemic wave and the estimated probability ratio (OR) as an independent variable was as follows: male/female (OR = 1.938; $P < 0.001$) and suicidal behavior (OR = 2.410; $P < 0.001$) (Table 5).

DISCUSSION

Our results showed that, in patients with mild and moderate mental illness, during the first wave and the adoption of the first set of measures to contain the pandemic spread, some protective factors seemed to balance and outweigh the risky ones related to the pandemic and quarantine. The total number of hospitalizations at the GHPW decreased with a relative increase in the pictures listed as a psychiatric emergency according to the MHT (codes 1 + 2). On the other hand, the acute relapse of acute

Table 2 Absolute numbers of total admissions, proportion of emergencies, urgencies and compulsory admissions occurred during the first pandemic wave and in the same period of previous 3 years

Yr	Total admissions	Urgencies	Emergencies (*P* value *vs* 2020)	Compulsory admissions (*P* value *vs* 2020)	Schizophrenia spectrum disorders (*P* value *vs* 2020)	Mood disorders (*P* value *vs* 2020)	Anxiety disorders (*P* value *vs* 2020)
2017	63	85.7%	14.3% (< 0.01)	7.2% (< 0.01)	25.1% (< 0.01)	28.2% (> 0.05)	5.8% (> 0.05)
2018	68	75.0 %	25% (< 0.05)	13.3% (< 0.05)	31.5% (< 0.05)	28.0% (> 0.05)	5.9% (> 0.05)
2019	81	86.4%	13.6% (< 0.01)	10.1% (< 0.05)	32.1% (< 0.05)	27.9% (> 0.05)	5.2% (> 0.05)
2020	47	71.8%	28.2%	19.7%	39.5%	28.6%	8.0%

Emergencies defined for codes 1 + 2, Urgencies defined for codes 3 + 4 + 5 at Mental health Triage. Diagnosis DSM-5 295.9-295.40-295.70-297.1-297.3-298.8-298.9: Schizophrenia Spectrum and Other Psychotic Disorders. Diagnosis DSM-5 296.2-296.3-296.9-311-296.XX: Bipolar and Related Disorders and Depressive Disorders. Diagnosis DSM-5 309.81-308.3-309.0-309.24-309.28-309.3-309.4-309.9-309.89: Anxiety Disorders and Trauma- and Stressor-Related Disorders.

Table 3 Multivariate logistic regression analyses: odds ratio, and 95% confidence interval for hospitalization during the first pandemic wave

Characteristic	*P* value	OR	95%CI for EXP
Male/female	< 0.001	1.754	1.331–2.312
Self-harm behaviour	< 0.001	2.066	1.477–2.890

CI: Confidence interval; OR: Odds ratio.

Table 4 Absolute numbers of total admissions, proportion of urgencies, emergencies and compulsory admissions occurred during the second pandemic wave and in the same period of the previous 3 yr

Yr	Total admissions	Urgencies	Emergencies (*P* value *vs* 2020/2021)	Compulsory admissions (*P* value *vs* 2020/2021)	Psychotic spectrum disorders (*P* value *vs* 2020/2021)	Affective spectrum disorders (*P* value *vs* 2020/2021)	Anxiety spectrum disorders (*P* value *vs* 2020/2021)
2017	88	80.7%	19.3% (> 0.05)	9.1% (> 0.05)	35.9% (> 0.05)	30.1% (< 0.05)	4.1% (< 0.01)
2018	85	81.2 %	18.8% (> 0.05)	10.7% (> 0.05)	35.6% (> 0.05)	29.4% (< 0.05)	3.7% (< 0.01)
2019	89	81.5%	18.5% (> 0.05)	9.9% (> 0.05)	33.7% (> 0.05)	28.8% (< 0.01)	4.2% (< 0.01)
2020/2021	84	80.7%	19.3%	10.4%	36.1%	32.9%	9.0%

Emergencies defined for codes 1 + 2, Urgencies defined for codes 3 + 4 + 5 at Mental health Triage. Diagnosis DSM-5 295.9-295.40-295.70-297.1-297.3-298.8-298.9: Schizophrenia Spectrum and Other Psychotic Disorders. Diagnosis DSM-5 296.2-296.3-296.9-311-296.XX: Bipolar and Related Disorders and Depressive Disorders. Diagnosis DSM-5 309.81-308.3-309.0-309.24-309.28-309.3-309.4-309.9-309.89: Anxiety Disorders and Trauma- and Stressor-Related Disorders

psychiatric clinical pictures belonging to schizophrenic spectrum disorders has undergone a statistically significant increase during the first pandemic wave and the first social restriction measures. In the literature, other authors have already described the increase in incidence rates of psychotic clinical pictures, and this phenomenon may probably have a generalizable value in all the countries most severely affected by the SARS-CoV-2-related pandemic and which have been subject to measures to contain the spread of the virus[24-26]. These preliminary data were consistent with results from other countries, such as China, where the pandemic would have originated and where the highest incidence of the first psychotic episode was reported in the months following the origin of the pandemic[27].

Table 5 Multivariate logistic regression analyses: odds ratio, and 95% confidence interval for hospitalization during the first pandemic wave

Characteristic	*P* value	OR	95%CI for EXP
Male/female	< 0.001	1.938	1.357–2.766
Self-harm behaviour	< 0.001	2.410	1.731–3.354

CI: Confidence interval; OR: Odds ratio.

It can be argued that the highly stressful scenario deriving from the fear of contagion, the confinement and the reduction of freedom imposed by the restrictive measures, the fear of the future evolution of the pandemic situation, the fear of the potential economic crisis could have played a significant role in the new-onset and the exacerbation of pathologies belonging to the schizophrenia spectrum according to international literature.

Although the relationship between the pressure exerted by highly stressful events during adult life and the onset of psychosis has been poorly studied, the results of a large meta-analysis suggest that the risk of psychosis onset is three times higher in subjects exposed to highly stressful events[28].

The data relating to the increase in the onset of new psychoses recorded in our data collection during the first pandemic wave was consistent with Pollice *et al*[29] in 2012. They observed the same boost in first psychosis episodes in connection with the earthquake in L'Aquila in 2009, an event whose traumatic extent can be compared, in some ways, to the traumatic impact of the related SARS-CoV-2 pandemic and to the consequent deterioration of social life and which share the same cultural scenario (both the stress events and the related results happened in Italy)[29].

We hypothesized that the coping strategy could be called into question to understand better the phenomenon from a psychological point of view in the biopsychosocial perspective.

Coping is identified as a complex of strategies adopted to manage stress better and reduce the emotional impact of stress events. They have been described as emotion-focused coping strategies, problem-oriented coping strategies and avoidance-focused coping strategies. Problem-focused coping strategies are termed "positive coping" as they relate to better outcomes[30]. Patients with more severe symptoms of schizophrenia are characterized by a reduced use of positive coping strategies[30]. Furthermore, the severity of psychotic symptoms is inversely related to positive coping, which is related to better functional outcomes[31,32]. Overall, results from the scientific literature suggest that schizophrenic patients rely on maladaptive coping strategies or have the potential to exacerbate distress.

The observation, already reported, of a global decline in the number of hospitalizations at "Maggiore" Bologna Hospital's GHPW also may be analyzed considering the theory of coping strategies. If several social factors such as the shared experience at the national level of a sense of cohesion, trust and social compassion perceived by the whole nation and the increase of the importance of informal social networks, it can also be argued that most individuals have adopted positive coping strategies. It could mean that individuals with a higher vulnerability to psychotic disorders cannot adopt on their own problem-oriented coping strategies. From the biological point of view of the biopsychosocial model of psychiatric disorders, it can be speculated that severe psychiatric pictures, including schizophrenia, bipolar disorders, and depressive disorders for which a greater etiological weight is recognized to the biological factor in the biopsychosocial model, could have been triggered by the direct neuroinvasiveness of SARS-CoV-2 or by the consequences of consequences of peripheral infection or by the subsequent inflammatory state on the central nervous system (CNS). Our group proposed a generating hypothesis that SARS-CoV-2 would demonstrate a neuroinvasive and neurotropic capacity through different anatomical pathways[33] through the angiotensin-converting enzyme-2 receptor. Possible speculation regarding the observed data is that SARS-CoV-2, through the colonization of the CNS, may act as an etiological cofactor in the exacerbation or in the onset of psychopathological pictures that recognize a more significant causal load of the biological component in the biopsychosocial model.

Further evidence of the present study suggests that in the medium to long term, such as during the adoption of restrictive measures in the second pandemic wave, there was an overall increase in the incidence of acute psychopathological relapse.

Indeed, the hospitalization rate reverted to the pre-existing incidence recorded in the same periods of the previous 3 years. This feature was mainly due to the rise of Mood (bipolar and related disorders and depressive disorders) and anxiety disorders. This result suggests that positive coping strategies, in the case of the ongoing pandemic, have proven to be effective in the short-term prevention of acute mood and anxiety disorders but have lost this in the long term. Other notable data is the increase in the suicidal behavior rate. This finding can be, in part, explained considering the increase of depressive disorders incidence.

On the other hand, the impact of the stress on suicidal behavior can also be considered. Indeed, as highlighted by Monica Starkman, in a brief report on the suicide attempt rate after the terrorist attack in September 11, 2001, the stress related to that unprecedented attack contributed to the statistically significant increase in the number of suicidal behaviors during the 2 years following the September 11, 2001[34]. Furthermore, in our study, suicidal behaviors are also strong predictors of psychiatric hospitalization during the second pandemic wave at multiple regression analysis.

CONCLUSION

The findings in this study showed that the higher incidence of hospitalizations for mood disorders and suicidal behavior must also be evaluated considering the growing and looming economic crisis due to the restrictive policy measures influencing the indicators of social well-being. Deaths from suicidal behavior increase dramatically during economic crises. In 2016, as Merzagora *et al*[35], in Italy, suicides increased between 2011 and 2016, during and immediately after the severe economic crisis that began in 2008[35]. Our preliminary data highlight the requirement to adopt preventive social and health policies to contain a potential "psychopathological pandemic" following the SARS-CoV-2 pandemic and invite the scientific society to pay attention to the problem.

By combining our clinical observations with the epistemological theories present in the literature[36-38], we propose an opinion hypothesis based on applying, to the phenomenon of psychological stress and coping strategies, the same laws of physics as the law by Hooke. It states that, in a mechanical system, the elastic response to a force F applied to an object is proportional to the variation of variable length (ΔL) multiplied by a specific constant of the material of which the object is composed [$F = \Delta L \cdot K$]. In biological systems, as reported by Kültz and Somero[38], organisms represent homeostatic systems in continuous dynamic equilibrium. Stress is constantly fluctuating around the norm throughout the life history of any organism. This fluctuation can push psychological and physiological set points out of homeostasis H.

The extent of the deviation (increase or decrease in value) of the most critical (limiting) variables (ΔHc) from the homeostatic set point (Hc) determines the behavior of the system. Therefore, for biological systems, Hooke's law can be defined as [$F = \Delta Hc \cdot k$], where k is a constant describing the phenotype of the biological system at the moment of exposure to force F and Hc represents the homeostatic norm H of most critical (limiting) physiological variables c. Our opinion is that this construct is also valid for psychological systems where homeostasis is ensured by multiple factors, including coping and stress response strategies. The challenge is to identify which biopsychological variables might be the most critical and limiting ones. These variables will depend on stress type and severity and the individual's state at the time of the stressful event. Within this theoretical hypothesis, the time factor would also play a key role. If a perturbing event acts for a time interval Δt, some psychological homeostatic set points could alter at different time points, depending on the "elastic capacity" of the same set points and the coping strategies adopted. In our case, the set point of the affective dimension would have "broken" later than that of the psychotic dimension.

Limits and perspectives of the study

The current study had several limitations. Meanwhile, it is a monocentric study and describes what happened in one of the Italian GHPWs. As such, it does not claim to draw ecumenical conclusions. Our data are consistent with what was described by other authors during the first pandemic wave. However, our study represents the first that follows diachronically, during the first and second pandemic waves, the trend of hospitalizations for acute psychiatric relapse in response to the Trauma of the pandemic and the consequent restrictive measures. The last "take-home messages" that deserve to be taken into consideration and on which to calibrate the subsequent

research trajectories are the following: The severe mental illnesses have not suffered, contrary to the moderate-mild mental disorders, a contraction in terms of acute relapse, during the first SARS-CoV-2 pandemic wave. The "advantage" of moderate/mild disorders is lost during the second pandemic because the protective factors probably no longer balance the precipitating factors. The findings from the first pandemic wave suggest that mild/moderate psychopathological clinical pictures can be successfully treated in settings other than GHPWs. This key point indicates that: It is possible to reduce hospitalization rates by enhancing and customizing the offers of the community mental health care settings; it is confirmed that traumatic experiences are important causal factors of psychotic relapse in the short-term period and mood disorders relapse in the long-term period; and the suicide risk could, with every reasonable probability, become the real post-pandemic emergency in light of the emerging and consequent economic-financial crisis.

ARTICLE HIGHLIGHTS

Research background

Significant consequences on mental health characterize unprecedented events like the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Therefore, variations in psychiatric hospitalization rates represent significant "sentinel events" for assessing the mental health response to stress. Responses to the stress may lead to new-onset or relapses of severe mental illness and suicidal behavior rates.

Research motivation

To reduce the further consequences on the mental health of the SARS-CoV-2 Pandemic by describing the repercussions of the first two waves of the pandemic on the psychiatric new-onset or relapse pictures rates.

Research objectives

The present study investigates any differences in terms of acute psychiatric relapse or new onset of psychiatric disorders observed at the General Hospital Psychiatric Ward (GHPW) at "Maggiore" Hospital in Bologna between the first and second epidemic.

Research methods

We took into consideration: Voluntary hospitalization rates, compulsory hospitalization rates, diagnoses, and the severity of psychopathological-clinical pictures estimated by the mental health triage and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition interview. Multiple logistic regression analyses were performed to estimate the correlation between the frequencies of the hospitalization and the frequencies of the independent variables.

Research results

The total admissions rate at GHPW decreased during the first SARS-CoV-2 pandemic wave compared to the same period throughout the 3 previous years. The compulsory admission rate and acute psychotic relapse rate increased during the first SARS-CoV-2 pandemic wave in comparison with the 3 previous years. During the second SARS-CoV-2 pandemic wave the total psychiatric admission rate reached the same ratio recorded during the same period of the previous 3 years. Suicidal behaviors, depressive disorders, bipolar disorders, anxiety spectrum disorders and trauma- and stressor-related disorders relapse arose among hospitalized patients during the second SARS-CoV-2 pandemic wave compared with the 3 previous years.

Research conclusions

We hypothesize that problem-focused coping strategies may be protective for the risk of acute psychopathological relapse in the short term but not in the medium-long term.

Research perspectives

The suicidal rate could arise in the future, after the first two pandemic waves therefore may be important to survey it and to adopt preventive strategies.

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World Journal of Psychiatry

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World J Psychiatr 2021 November 19; 11(11): 1106-1115

DOI: 10.5498/wjp.v11.i11.1106

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Self-compassion and resilience mediate the relationship between childhood exposure to domestic violence and posttraumatic growth/stress disorder during COVID-19 pandemic

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Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Medical Department of Shenzhen University (Approval No. 2020005).

Informed consent statement:

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Abstract

BACKGROUND

Studies have indicated that childhood exposure to domestic violence is a common factor in posttraumatic growth (PTG) and posttraumatic stress disorder (PTSD), but it is unclear whether PTG and PTSD share a common/different underlying mechanism.

AIM

To explore the common/different underlying mechanism of PTG and PTSD.

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at liyezou123@gmail.com. Participants gave informed consent for data sharing

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

Country/Territory of origin: China

Specialty type: Psychology

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

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Received: February 11, 2021
Peer-review started: February 11, 2021
First decision: March 16, 2021

METHODS

Between February 12 and 17, 2020, a nationwide cross-sectional online survey was conducted in China among 2038 university students, and a self-administered questionnaire was used for the data collection. The data included demographic characteristics, such as age, gender, and subjective social economic status, and childhood exposure to domestic violence scale that was selected from the Chinese version of revised Adverse Childhood Experiences Question, Self-compassion Scale, Connor–Davidson Resilience Scale, Posttraumatic Growth Inventory, and the Abbreviated PTSD Checklist-Civilian version. A structural equation model was used to test the hypotheses.

RESULTS

Exposure to domestic violence was significantly associated with PTG and PTSD *via* a 1-step indirect path of self-compassion (PTG: β = -0.023, 95%CI: -0.44 to -0.007; PTSD: β = 0.008, 95%CI: 0.002, 0.014) and *via* a 2-step indirect path from self-compassion to resilience (PTG: β = -0.008, 95%CI: -0.018 to -0.002; PTSD: β = 0.013, 95%CI: 0.004-0.024). However, resilience did not mediate the relationship between exposure to domestic violence and PTG and PTSD.

CONCLUSION

PTG and PTSD are common results of childhood exposure to domestic violence, which may be influenced by self-compassion and resilience.

Key Words: Self-compassion; Resilience; Domestic violence; Posttraumatic growth; Posttraumatic stress disorder; COVID-19

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Core Tip: The present study explored the issue that whether posttraumatic growth (PTG) and PT stress disorder (PTSD) have a common underlying mechanism *via* self-compassion and resilience. This is the first study that examined the mechanisms underlying the association of domestic violence with PTG and PTSD among college students during the coronavirus disease-2019 pandemic, providing insights into the development of PTG and PTSD in the context of a global pandemic, which emphasize unique psychosocial dynamics.

Citation: Chi XL, Huang QM, Liu XF, Huang LY, Hu MJ, Chen ZJ, Jiao C, Stubbs B, Hossain MM, Zou LY. Self-compassion and resilience mediate the relationship between childhood exposure to domestic violence and posttraumatic growth/stress disorder during COVID-19 pandemic. *World J Psychiatr* 2021; 11(11): 1106-1115
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1106.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1106

INTRODUCTION

Domestic violence has always been a serious social problem with a high incidence rate. Data from the World Health Organization[1] indicate that one-third of women worldwide have experienced physical violence, with many of these incidents happening in front of children and adolescents, therefore making it even more disturbing. Previous studies have consistently demonstrated that children who were exposed to domestic violence are significantly associated with an increased risk of psychological problems such as posttraumatic stress disorder (PTSD)[2-4].

Although PTSD symptoms in posttraumatic (PT) adolescent groups have been reported, many researchers found that PT individuals may also show positive psychological changes or posttraumatic growth (PTG)[5-7], which is defined as the positive psychological changes experienced as a result of the struggle with a traumatic event.

PTSD and PTG following trauma are two completely different psychological constructs but may coexist in traumatized individuals, especially individuals who were exposed to domestic violence[8,9]. However, few studies have simultaneously

Revised: May 2, 2021
Accepted: July 16, 2021
Article in press: July 16, 2021
Published online: November 19, 2021

P-Reviewer: Kurniawan A, Tung TH
S-Editor: Zhang H
L-Editor: Wang TQ
P-Editor: Ma YJ

examined the mechanisms by which domestic violence affects PTG and PTSD. Therefore, it is unclear whether a common mechanism underlies the association between domestic violence and PTG/PTSD. To better understand the process of reactions to stressful events among young adults and to develop prevention or intervention programs, this study aimed to identify factors that mediate the association between physical domestic violence and PTG and PTSD. This study further examined and compared the mechanisms underlying these associations. It may inform future mental health interventions for vulnerable individuals. In addition, this study has critical significance as it was conducted amidst the coronavirus disease 2019 (COVID-19) outbreak, thus it may provide insights into the development of PTG and PTSD in the context of a global pandemic. Such insights emphasize unique psychosocial dynamics, especially among those who experienced trauma in the past and those currently experiencing global psychosocial stressors attributable to the pandemic.

Potential mediating role of self-compassion and resilience

The Kumpfer's resilience framework believes that individuals who encountered the traumatic event would gather their own resources to cope with the stress based on their cultural context. The more risk factors (such as childhood exposure to domestic violence) or the fewer protective factors in the cultural context there are, the higher probability individuals perform maladaptively, and *vice versa*. Hence, the stress would be alleviated or strengthened by the cultural context. Then, interactions between individuals and the environment would happen to handle stress, which may lead to the changes of the internal resources and traits associated with resilience. Consequently, the process of resilience influenced by such traits would bring about the adaption or maladaptation which may reduce the possibility of developing PTG and PTSD[10].

Self-compassion is the ability to treat oneself with the same kindness and compassion as one would treat others in the same situation[11] , which was regarded as a trait associated with resilience. Existing literature indicated that self-compassion is an important predictor of resilience and promoting self-compassion may facilitate individual resilience[12-14]. This suggests that individuals with high self-compassion can exhibit a higher level of resilience and better adapt and recover when facing stress or difficulties. In contrast, individuals with a low level of self-compassion are inclined to criticize or reject themselves, which often form negative self-beliefs and low self-esteem, and feel unworthy of love[15]. These eventually lead to a low level of resilience.

Present study

Based on the Kumpfer's resilience framework and empirical evidence, the present study hypothesized that the effect of childhood exposure to domestic violence on PTG and PTSD is significantly mediated by self-compassion (hypothesis 1) and resilience (hypothesis 2), respectively (1-step indirect path). It was also hypothesized that childhood exposure to domestic violence may affect PTG and PTSD *via* self-compassion to resilience (hypothesis 3) (2-step indirect path). Specifically, suffering from the trauma of COVID-19, children and adolescents who were exposed to domestic violence regarded as a risk factor may show a lower level of self-compassion compared with those who were not. It would lead to a lower level of resilience, increased risk of PTSD, and decreased likelihood of PTG.

MATERIALS AND METHODS

Study participants

Between February 12 and 17, 2020, college students who have been or have not been exposed to domestic violence from more than 180 universities in China were recruited to participate in this study. Prior to filling out several self-reported questionnaires, all volunteers signed an online consent form which was opaque about the aim of the study to control the hawthorn effect. Overall, 2500 students from 29 provinces and cities of China were invited on the basis of the following inclusion criteria: Being at least 18 years of age and fluent in Chinese; however, only 2126 students completed the questionnaire (85.04% response rate). Of these 2126 students, 88 were excluded due to missing or incomplete responses. Finally, data of the remaining 2038 students (755 males and 1283 females, mean age: 20.56 ± 1.90) was analyzed. To ensure the adequate power, we calculated the sample size using the sampling formula {$N = [(Z^2)p(1-p)]/d^2$}

[16], which determined that at α = 0.05, P = 0.3, and d = 0.03, the sample size needed was approximately 896 individuals. The sample size of 2038 in the present study should be sufficient.

Procedure

In an attempt to control the pandemic, the government had imposed a nationwide lockdown. Hence, this cross-sectional survey was conducted online, which was also safer and convenient. For 6 d, students were invited to participate in the survey *via* Tencent's QQ, WeChat, Weibo, and college-related websites, such as university association websites and bulletin board system forums. Participants who clicked the survey link would be automatically directed to the questionnaire website page. It would not be proceeded to the next page unless participants completed all the items on the current page so that there was no missing data for those who completed the questionnaire. Participants received 10 RMB *via* online payment (equivalent to USD 1.5 at the time) on completion of the survey, which took approximately 20 min. Recruitment and data collection procedures were approved by the Human Research Ethics Committee (No: 2020005) of Shenzhen University.

Measurement

Dependent variables: The independent variables were PTSD and PTG. PTSD symptoms were assessed using the abbreviated PTSD Checklist-Civilian version (PCL-C)[17,18]. It consists of six items that correspond to six different symptoms. The respondents rated the frequencies of symptoms over the past 1 mo on a 5-point Likert scale that ranges from 1 (not at all) to 5 (extremely). To assess participants' PTSD related to the COVID-19 pandemic, we revised "stressful experience" in this scale to "COVID-19 pandemic" (*e.g.*, "Feeling very upset when something reminded you of COVID-19 pandemic from the past"). Higher total scores indicate more severe PTSD symptoms. The PCL-C possesses good psychometric with a sensitivity of 0.78 and specificity of 0.71[17]. In the present study, the results indicated a good internal reliability (Cronbach's α = 0.81) of this scale.

PTG was assessed using the 21-item Posttraumatic Growth Inventory (PTGI)[19]. It includes five dimensions: Relating to others (seven items), new possibilities (five items), personal strength (four items), spiritual change (two items), and appreciation of life (three items). Previous studies conducted by two different research groups indicated that few persons, including Chinese college students, expressed religious beliefs and spiritual change (two items); therefore, these items were deemed not applicable to the local culture and were finally excluded from this study[20,21]. All items were rated on a 6-point scale ranging from 0 (no change) to 5 (complete change). Sum scores were obtained, ranging from 0 to 95, with higher scores representing higher levels of PTG. The inventory in prior studies was found to have good psychometric properties in the Chinese context with an internal reliability of 0.88[22-24]. In this study, the internal reliability of the inventory was 0.95 and the internal reliabilities for the 4 subscales were 0.88, 0.86, 0.81, and 0.82, respectively.

Independent variable: The independent variable was childhood exposure to domestic violence, which was selected from the Chinese version of the revised Adverse Childhood Experiences Question. More specifically, this scale was used to measure domestic violence experienced in the first 18 years of life[25,26]. It contains 4 items and each item was rated on a 5-point scale ranging from 1 to 5 (1 = never, 2 = once or twice, 3 = sometimes, 4 = often, and 5 = very often). The total scores were used, with higher scores representing a higher frequency of exposure to domestic violence. The Chinese version of the revised Adverse Childhood Experiences Question possesses good psychometric properties with an internal reliability of 0.83[26]. In this study, the internal reliability of the scale was good (Cronbach's α = 0.84).

Mediation variables: The mediation variables were self-compassion and resilience. Self-compassion was assessed using the Self-compassion Scale, which has 26 items on 6 dimensions: Self-kindness (5 items), self-judgment (5 items), common humanity (4 items), isolation (4 items), mindfulness (4 items), and over-identification (4 items). All items were rated on a 5-point scale ranging from 1 (almost never) to 5 (almost always). Self-judgment, isolation, and over-identification should be scored in reverse, then a grand mean was computed based on the mean of all six subscales, with higher scores reflecting a greater level of self-compassion. This scale was adapted in Chinese, with good reliability (Cronbach's α = 0.96) and validity reported among Chinese adolescents and college students[27-29]. In this study, the internal reliability of the scale was good (Cronbach's α = 0.87), and the internal reliabilities for the 6 subscales

were 0.81, 0.65, 0.68, 0.75, 0.81, and 0.66, respectively, indicating an acceptable reliability.

Resilience was assessed using a short version of the Connor–Davidson Resilience Scale (CD-RISC). It reflects the ability to tolerate experiences, such as change, personal problems, illness, pressure, failure, and painful feeling[30]. Participants responded to 10 items on a 5-point Likert scale (0 = not true at all to 4 = true nearly all of the time), with total scores ranging from 0 to 40 (higher points indicate greater resilience capacity). This original scale in Chinese was adapted and reported with good reliability (Cronbach's α = 0.88) and validity[31,32]. In this study, the results indicated an excellent internal consistency (Cronbach's α = 0.92).

Statistical analysis

First, the mean ± SD or distribution was calculated for all variables. Second, partial correlations were performed to examine the association between domestic violence and PTG, PTSD, self-compassion, and resilience while controlling the age, gender, subjective social economic status, and family structure. Third, to examine the mediating role of self-compassion and resilience in the relationship between domestic violence and PTG and PTSD, a series of structural equation models were built. First, we established a direct model from domestic violence to PTG and PTSD and relational paths among PTG and PTSD were then added. Second, based on the direct model, an indirect model with the mediators (self-compassion and resilience) inserted between domestic violence and PTG and PTSD was built. In this indirect model, the predictive paths from self-compassion to resilience were added. The specific mediation pathways were presented as below: domestic violence → self-compassion → resilience → PTG/PTSD; domestic violence → resilience → PTG/PTSD; domestic violence → self-compassion → PTG/PTSD. Finally, a parsimonious model constraining non-significant paths to zero was built to further identify the indirect effect of domestic violence and PTG/PTSD *via* self-compassion and resilience. In the process of path analysis, all aforementioned variables were treated as observed variables in terms of their total scores, with controlling the cofounders as above. For all pathways, standardized direct, specific indirect, total indirect, and total effects were estimated. Standardized values were reported for all estimations. The goodness of fit was assessed using the following fit indices: Comparative fit index (CFI), Tucker-Lewis index (TLI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). Thresholds used were as follows: For CFI and TLI, excellent fit > 0.95 and moderate fit > 0.90; for RMSEA and SRMR, excellent fit < 0.05 and moderate fit < 0.08.

RESULTS

Descriptive statistics and correlations of variables

The descriptions of cofounders are as follows: Gender, 755 males and 1286 females; age, 20.56 (SD = 1.90) years; subjective social economic status, 4.85 (SD = 1.38); family structure, 1859 intact families and 179 non-intact families. Table 1 shows the mean ± SD for all variables, as well as results from partial correlation analyses between every two variables (domestic violence, self-compassion, resilience, PTG, and PTSD). The mean variable values were as follows: PTG, 60.97 (SD = 16.95); PTSD, 11.79 (SD = 4.25); resilience, 35.45 (SD = 6.62); self-compassion, 84.75 (SD = 11.88); and domestic violence, 4.76 (SD = 1.72). Further, the results of partial correlations while controlling the age, gender, subjective social economic status, and family structure, showed that PTG was significantly positively correlated with self-compassion and resilience (P < 0.001), but significantly negatively correlated with domestic violence (P < 0.001). Moreover, PTSD had a positive association with domestic violence (P < 0.001), but negatively correlated with resilience and self-compassion (P < 0.001). Similarly, resilience was significantly positively correlated with self-compassion (P < 0.001), whereas resilience and self-compassion were negatively correlated with domestic violence (P < 0.001).

Indirect effect analysis

First, the results indicated that domestic violence had a direct effect on PTG and PTSD. This model fits the data better (χ^2 = 424.026, df = 49, P = 0.000, CFI = 0.966, TLI = 0.951; RMSEA = 0.061, 90%CI (0.056, 0.067), SRMR = 0.024), while controlling the age, gender, subjective social economic status, and family structure. Results from the path

Table 1 Descriptive statistics and correlation analyses among posttraumatic growth, posttraumatic stress disorder domestic violence, self-compassion, and resilience

Variable	mean ± SD	1	2	3	4	5
PTG	60.97 ± 16.95	1				
PTSD	11.79 ± 4.25	0.02	1			
Resilience	35.45 ± 6.62	0.32[c]	-0.28[c]	1		
Self-compassion	84.75 ± 11.88	0.33[c]	-0.34[c]	0.56[c]	1	
Domestic violence	4.77 ± 1.72	-0.10[c]	0.09[c]	-0.08[c]	-0.56[c]	1

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.

analysis showed that domestic violence was negatively associated with PTG (β = -0.100, 95%CI: 0.147 to -0.052, $P < 0.001$) and positively associated with PTSD (β = 0.083, 95%CI: 0.033 to 0.135, $P < 0.005$). This indicated that domestic violence was a common factor in PTG and PTSD.

Based on the results of the direct effect model, an indirect effect model was established controlling the cofounders as above. The results indicated a complete model with fit indices as follows: χ^2 = 891.522, *df* = 128, $P < 0.001$, CFI = 0.960, TLI = 0.943; RMSEA = 0.054, 90%CI (0.051-0.057), SRMR = 0.045. The path analysis showed that the paths between domestic violence and resilience were non-significant, and the remaining paths were statistically significant. Next, we removed the non-significant path above; constraining these paths to zero caused no degradation in fit. Using these procedures, a parsimonious model was built (Figure 1) controlling the cofounders as above. The result also indicated a good model with the following fit indices: χ^2 = 891.564, *df* = 129, $P = 0.000$, CFI = 0.960, TLI = 0.943; RMSEA = 0.054, 90%CI (0.051 to 0.057), SRMR = 0.045. The path analysis showed that domestic violence was significantly negatively related to PTG *via* a 1-step indirect path of self-compassion (β = -0.023, 95%CI: -0.044 to -0.007, $P < 0.01$) and by one 2-step indirect path of self-compassion to resilience (β = -0.008, 95%CI: -0.018 to -0.002, $P < 0.05$). Domestic violence was significantly positively related to PTSD *via* a 1-step indirect path of self-compassion (β = 0.008, 95%CI: 0.002 to 0.021, $P < 0.07$) and by one 2-step indirect path of self-compassion to resilience (β = 0.013, 95%CI: 0.004 to 0.024, $P < 0.01$). The detailed information is listed in Table 2. These findings suggest that self-compassion to resilience mediates the relationship between domestic violence and PTG and PTSD and that the mechanisms underlying the association between domestic violence and PTG and PTSD are similar.

DISCUSSION

This study examined the mechanisms underlying the relationship between childhood exposure to domestic violence and PTG and PTSD among Chinese college students during the COVID-19 pandemic. The findings of this study indicated that childhood exposure to domestic violence was significantly associated with PTG and PTSD[4,20]. Furthermore, these associations were significantly mediated by self-compassion (1-step indirect path) and from self-compassion to resilience (2-step indirect path). These results suggested that there were similar indirect paths from childhood exposure to domestic violence to PTSD and PTG. Possible explanations for these results are elaborated below.

First, childhood exposure to domestic violence was directly associated with PTG and PTSD, which further supports Kumpfer's resilience framework. According to the theory, when individuals are under stress, those with more protective factors can easier get through the crisis, but those with more risk factors may become maladaptive.

Furthermore, this study found that childhood exposure to domestic violence had a positive association with PTSD and a negative association with PTG *via* a 1-step indirect path of self-compassion (supported hypothesis 1). Individuals with high self-compassion are more likely to pay attention to the positive aspects of the struggle with

Table 2 Bootstrapping indirect effect and 95% confidence interval for multiple mediation model

Indirect effect	Estimated effect	95%CI	Relative mediation effect
Dependent variable: PTG			
Total indirect	-0.032[b]	(-0.055, -0.010)	32.99%
Specific indirect 1	0.000	(-0.006, 0.004)	0%
Specific indirect 2	-0.023[b]	(-0.044, -0.007)	23.71%
Specific indirect 3	-0.008[a]	(-0.018, -0.002)	8.25%
Dependent variable: PTSD			
Total indirect	0.022[b]	(0.007, 0.039)	28.95%
Specific indirect 1	0.001	(-0.007,0.008)	1.32%
Specific indirect 2	0.008[a]	(0.002, 0.021)	10.53%
Specific indirect 3	0.013[b]	(0.004, 0.024)	17.11%

n = 2038. Bootstrap sample size = 5000.
[a]P < 0.05.
[b]P < 0.01.
[c]P < 0.001.
Total indirect: domestic violence → posttraumatic growth/posttraumatic stress disorder (PTG/ PTSD); Specific indirect 1: domestic violence → resilience → PTG/PTSD; Specific indirect 2: domestic violence → self-compassion → PTG/PTSD; Specific indirect 3: domestic violence → self-compassion → resilience → PTG/PTSD. PTG: Posttraumatic growth; PTSD: Posttraumatic stress disorder.

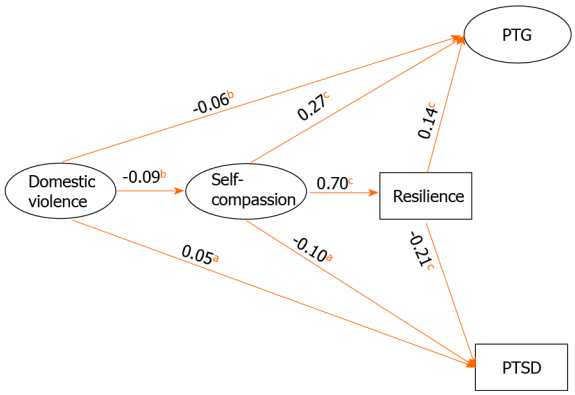


Figure 1 Multiple indirect effects model after controlling age, gender, subjective social economic status, and family structure. [a]P < 0.05, [b]P < 0.01, [c]P < 0.001. PTG: Posttraumatic growth; PTSD: Posttraumatic stress disorder.

trauma and positively reframe their understanding of the PT world[8]. These strategies can be used to help adolescents find meaning, recover from negative emotions, and realize PTG, and *vice versa*[21]. Additionally, we identified a 2-step indirect path from domestic violence to PTG and PTSD *via* from self-compassion to resilience, which was consistent with hypothesis 3. When facing challenges, individuals with more exposure to domestic violence in their childhood are less likely to be self-compassionate and lead to lower resilience. By contrast, adolescents who are more self-compassionate tend to be resilient and "bounce back" from challenges[33]. This process may reduce PTSD symptoms and promote PTG[34,35]. During the COVID-19 outbreak, individuals with a lower level of self-compassion and resilience may find it more difficult to cope with the stressful event, compared to those with a higher level of self-compassion and resilience. This may eventually lead to PTSD symptoms and reduce the possibility of PTG[36].

Of note, childhood exposure to domestic violence had non-significant effects on PTG and PTSD using a 1-step indirect path *via* resilience. Taking a closer look, the relationship between childhood exposure to domestic violence and resilience were not significantly correlated, which could be attributed to the fact that resilience is a dynamic development process, accorded with the latest academically accepted definition that it refers to an individual's efforts to adjust and actively adapt under

stress on the one hand instead of a steady trait[37]. Besides, it emphasizes an individual's adaptive outcome on the other hand. Thereby, the profile of resilience at one measurement time cannot fully represent the dynamic process.

CONCLUSION

This study has several limitations. First, findings from the self-reported scales need further confirmation, using data from clinical interviews that can determine the presence of being diagnosed with PTSD. Second, the study employed a cross-sectional design, and the corresponding data before the COVID-19 outbreak was not available, thus limiting the causal interpretation of the findings. Thus, a latent profile transition analysis may be conducted within a longitudinal study to examine the developmental trajectory and longitudinal predicting mechanism of PTSD and PTG throughout the COVID-19 outbreak. Third, psychopathological impacts of self-compassion and variations of developing self-compassion among individuals were not evaluated, which may have provided further insights on how PTG and PTSD are developed among individuals. However, this warrants future research. Fourth, due to the cross-sectional design, the participants have to recall their childhood experiences instead of reporting existing circumstances, which leads to the potency of recall bias.

Despite these limitations, this is an exploratory study that examined the mechanisms underlying the association of domestic violence with PTG and PTSD among college students during the COVID-19 pandemic. Findings indicate that domestic violence is common to both PTSD and PTG, which may explain the coexistence of PTG and PTSD in young adults. In addition, it suggests that domestic violence affects PTG and PTSD through similar underlying mechanisms. Self-compassion and resilience are individual's internal resources, which may increase the PTG and reduce the PTSD symptoms. From a clinical perspective, the unique roles of self-compassion and resilience in PTSD and PTG should be considered. Psychological services engaged to relieve PTSD and promote PTG should develop the competence of self-compassion and resilience of youth. The government should pay attention to domestic violence with timely and appropriate actions that should be taken: (1) Establish and improve the maternal and child protection system; (2) strengthen the support for community work to reduce the occurrence of domestic violence; (3) provide shelter for victims in the domestic violence during the epidemic period; and (4) form a public opinion environment against domestic violence.

ARTICLE HIGHLIGHTS

Research background

It was reported that domestic violence had a 30 percent incidence, which always happened in front of children or adolescents, causing an increased risk of psychological problems such as posttraumatic stress disorder (PTSD) symptoms. But some people who are exposed to domestic violence perform positive changes in psychology such as posttraumatic growth (PTG). It is unclear whether PTG and PTSD share a common underlying mechanism. The present study is exploratory to reveal it during the coronavirus disease 2019 (COVID-19).

Research motivation

Based on the shattered world assumption theory, the PTG model, and conservation of resources theory, this study hypothesized that the self-compassion and resilience are the common factors for PTG and PTSD. The present study addressed the mediator roles of self-compassion and resilience. It may inform future mental health interventions for certain individuals.

Research objectives

The present study aimed to explore the common mechanism of PTG and PTSD, revealing the mediating role of self-compassion and resilience between exposure to domestic violence and PTG/PTSD.

Research methods

A nationwide cross-sectional online survey was conducted in China during the

COVID-19 pandemic. The data was collected using the Chinese version of revised Adverse Childhood Experiences Question, Self-compassion Scale, Connor-Davidson Resilience Scale, PT Growth Inventory, and the Abbreviated PTSD Checklist-Civilian version. A structural equation model was conducted to analyze the data.

Research results

The path analysis indicated that exposure to domestic violence was significantly correlated with PTG and PTSD *via* a 1-step indirect path of self-compassion and *via* a 2-step indirect path from self-compassion to resilience. The 1-step indirect path of resilience did not reach significance.

Research conclusions

PTG and PTSD share a common mechanism for those who were exposed to domestic violence. Those who perform a lower level of self-compassion would tend to difficultly bounce back to normal, causing an increased risk of PTSD and decreased possibility of PTG, and *vice versa*.

Research perspectives

From a clinical perspective, the intervention study could be considered in investigating the roles of self-compassion and resilience for vulnerable individuals.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 1116-1128

DOI: 10.5498/wjp.v11.i11.1116

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Subgrouping time-dependent prescribing patterns of first-onset major depressive episodes by psychotropics dissection

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Institutional review board statement: This study was approved by the research ethics committees of National Taiwan University Hospital, Taipei Municipal Wanfang Hospital, and Taipei City Hospital, Songde Branch.

Informed consent statement: All

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Abstract

BACKGROUND

Subgrouping patients with major depressive disorder is a promising solution for the issue of heterogeneity. However, the link between available subtypes and distinct pathological mechanisms is weak and yields disappointing results in clinical application.

AIM

To develop a novel approach for classification of patients with time-dependent prescription patterns at first onset in real-world settings.

METHODS

Drug-naive patients experiencing their first major depressive episode (n = 105) participated in this study. Psychotropic agents prescribed in the first 24 mo

study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no competing interests.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Supported by the Ministry of Science and Technology, Taiwan, No. MOST 107-2314-B-002-219 and No. MOST 108-2314-B-002-110-MY2; the National Taiwan University Hospital, No. UN110-021.

Country/Territory of origin: Taiwan

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: July 8, 2021
Peer-review started: July 8, 2021
First decision: July 28, 2021

following disease onset were recorded monthly and categorized as antidepressants, augmentation agents, and hypnosedatives. Monthly cumulative doses of agents in each category were converted into relevant equivalents. Four parameters were used to summarize the time-dependent prescription patterns for each psychotropic load: Stability, amount, frequency, and the time trend of monthly prescriptions. A K-means cluster analysis was used to derive subgroups of participants based on these input parameters of psychotropic agents across 24 mo. Clinical validity of the resulting data-driven clusters was compared using relevant severity indicators.

RESULTS

Four distinct clusters were derived from K-means analysis, which matches experts' consent: "Short-term antidepressants use", "long-term antidepressants use", "long-term antidepressants and sedatives use", and "long-term antidepressants, sedatives, and augmentation use". At the first 2 years of disease course, the four clusters differed on the number of antidepressants used at adequate dosage and duration, frequency of outpatient service use, and number of psychiatric admissions. After the first 2 years following disease onset, depression severity was differed in the four subgroups.

CONCLUSION

Our findings suggested a new approach to optimize the subgrouping of patients with major depressive disorder, which may assist future etiological and treatment response studies.

Key Words: First episode; Depression; Classification; Psychopharmacology; Depression treatment

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Core Tip: This study evaluated the time-dependent prescription patterns in drug-naive patients experiencing their first major depressive episode with data collected over the first 2 years after disease onset. The K-means clustering analysis was performed, along with the evaluation of four input parameters to generate data-based subgroups. Four feature-based clusters were identified, differentiated by the time-dependent prescription profiles and burden of the disease. Our novel parameters successfully captured the reciprocal interaction between physicians' prescriptions and disease status in a real-world setting. This study presents a novel clustering strategy that can be used to generate prescription-based subtypes.

Citation: Chen HC, Hsu HH, Lu ML, Huang MC, Chen CH, Wu TH, Mao WC, Hsiao CK, Kuo PH. Subgrouping time-dependent prescribing patterns of first-onset major depressive episodes by psychotropics dissection. *World J Psychiatr* 2021; 11(11): 1116-1128
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1116.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1116

INTRODUCTION

Major depressive disorder (MDD) is a common and challenging mental illness[1]. Even though research on the biological substrates of MDD is increasing, the heterogeneity of MDD substantially compromises the applicability of these study findings[2]. Thus, subgrouping MDD into homogeneous clusters, which could be used to investigate specific neurobiological and pathological mechanisms, is a promising solution for this.

A number of clinical features were previously used to subgroup MDD[3]. Most subtyping schemes (such as melancholic, psychotic, and atypical features) are based on differences in patterns of clinically observed characteristics. However, the link between these subtypes and distinct pathological mechanisms is weak and yields disappointing results in clinical application[3,4]. Even using data-driven latent class analyses, there is inadequate evidence to support the existence of symptom-based

Revised: August 5, 2021
Accepted: September 22, 2021
Article in press: September 22, 2021
Published online: November 19, 2021

P-Reviewer: Yao XF, Yu R
S-Editor: Fan JR
L-Editor: A
P-Editor: Guo X



subtypes[5]. The heterogeneity in MDD is derived from multiple aspects of the disease, including symptom presentation, clinical features, family history, comorbidities, phenotypic stability over time, and treatment response. With these complexities in mind, our goal was to identify the biologically relevant clusters of MDD. The fundamental scheme and analytical technique need to be enhanced to facilitate disease subtyping and improve the identification of the homogeneous clusters of MDD.

In this study, we developed a novel approach by clustering patients with similar biologically relevant potentials. Our approach was based on three conceptual aspects. First, parameters that were correlated with biological mechanisms were preferred to theoretical or symptom-based constructs. Second, non-descriptive parameters were considered superior to linguistic-defined symptoms. Third, creating parameters that enrich the available information helped sub-classify patients into data-driven clusters [6]. While practicing physicians commonly initiate treatment according to clinical guidelines, the ensuing adjustments to the regimen are essentially based on the temporal change of clinical response. The medication class and dose of prescribed psychotropics evolve naturally and reflect the underlying disease entity, as well as the patient's preference and treatment response at a given moment. The time-dependent change in regimen is dynamically determined by considering factors such as symptom profiles, clinical features, disease stage, treatment response, effectiveness and side effects of medications, and level of functional recovery[7]. As a result, we adopted a time-dependent prescription pattern in the early disease stage as the preferred indicator for MDD subgrouping.

In summary, we aimed to develop a novel approach to tackle the heterogeneity in drug-naive patients experiencing their first episode of MDD, using detailed prescription patterns of major psychotropic classes during the early disease course. Specifically, we developed new parameters to capture time-dependent information on prescription patterns in the first two years after the initial diagnosis. Using this information, we performed a K-means clustering analysis for data-driven subgrouping to yield empirical subtypes of MDD.

MATERIALS AND METHODS

Participants

This study used the cohort established by the Research Collaborating Group for New Insight, Strategy and Evaluation–Treatment-Resistant Depression Program (RECOGNISE-TRD program). Between October 2010 and April 2016, remitted individuals with a DSM-IV-TR diagnosis of MDD and between 18 and 65 years old were recruited to participate in this study[8]. Participants were eligible if they had more than 2 years of complete medical records from their first episode to the date of recruitment. The duration of the MDD course beyond the 2 years after onset to the date of recruitment differed between participants. The medical records should document all of the participants' psychiatric and medical history throughout the disease course, including prescriptions, use of outpatient and inpatient services, and information on their comorbidities. If participants discontinued their treatments within 2 years of disease onset because of full remission, they were contacted to ensure the absence of any depressive episode before recruitment. Participants were excluded if they had incomplete medical records, were comorbid with organic brain syndromes, dementia, substance abuse, psychotic disorders, and schizoaffective disorders or if their diagnosis had been revised to bipolar affective disorder. A total of 105 participants were eligible. This study was approved by the research ethics committees of National Taiwan University Hospital, Taipei Municipal Wanfang Hospital, and Taipei City Hospital, Songde Branch. Written informed consent was obtained from each participant. All methods were performed in accordance with the relevant guidelines and regulations.

Pharmacological dissection and the calculation of psychotropic loads

Three major classes of psychotropic agents are used to treat MDD, including antidepressants and adjunctive agents (augmentation agents and hypnosedatives). Following disease onset, the drug class, dosage, date of administration, and duration of prescription were recorded in 4-wk intervals. Since the natural course of a major depressive episode is usually between 6-13 mo[9], the present study evaluated the prescription pattern of psychotropics using monthly data collected over the first 2 years after disease onset. Observations collected over this period provided adequate time for patients to experience all treatment regimens suggested by the treatment

guidelines.

In this study, pharmacological dissection was used to categorize the psychotropic agents, including antidepressants, augmentation agents and hypnosedatives[10]. Antidepressants used in this study include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, mirtazapine, bupropion, moclobemide, and agomelatine. Augmentation agents included anticonvulsants, antipsychotics, lithium, thyroxin, and methylphenidate. All benzodiazepine receptor agonists (BzRA) were categorized as hypnosedatives. Cumulative doses of each psychotropic medication class were converted into equivalents and designated as antidepressant load (ADL), augmentation load (AUGL), and sedative load (SL). These three equivalent-based psychotropic loads have been used in the literature[10]. For each participant, the monthly cumulative equivalents for 3 classes of psychotropic loads were calculated in 4-wk intervals, starting with the initiation of treatment.

Doses of antidepressants and augmentation agents were transformed into equivalents using the Anatomical Therapeutic Chemical (ATC) system[11]. In analyzing hypnosedative use, equivalent doses of all BzRA were calculated, including benzodiazepines (BZDs) and the Z-drugs (zaleplon, zolpidem, zopiclone, and eszopiclone). As the defined daily dose in the ATC system for hypnosedatives do not adequately represent the clinical usage of BZDs as anxiolytics or hypnotics[12], the BZDs equivalents suggested by the Ashton manual were adopted in the present study [13]. Since conversion ratios for a number of BZD drugs commonly used in Taiwan are not provided in the original Ashton manual (including brotizolam, midazolam, oxazolam, and fludiazepam), study investigators defined the equivalents for these agents by consensus. The full list of BZD equivalents is provided in Supplementary Table 1.

Mental and physical comorbidities

In this study, anxiety disorders and physical comorbidities were incorporated as covariates in the multivariable models evaluating the differences in several clinical severity indicators between empirical clusters. The presence of an anxiety disorder was defined as more than three consecutive instances that matched the DSM-IV-TR diagnostic criteria during the first two years following MDD onset. Additionally, physical comorbidities were evaluated as the number of medical diseases identifiable using the Charlson comorbidity index[14].

Clinical severity indicators

Several domains of clinical severity were used to examine the validity of data-driven clusters. Firstly, the total number of prescribed antidepressants and the number of prescribed antidepressants with adequate dosage and adequate duration (ADAD) were calculated within the first two years after disease onset. The adequate dosage used was as per the dose suggested by the Ministry of Health and Welfare, Taiwan, for treating MDD[15]. An adequate duration was defined as at least two weeks of treatment[16,17]. Secondly, the cumulative frequency of patients' utilization of psychiatric facilities, including outpatient services and psychiatric admissions, were documented for within 2 years of disease onset and from 2 years after disease onset to the date of recruitment, respectively. Additionally, the severity of depression was scored on the recruitment date using the Chinese version of the Beck Depression Inventory-II (BDI-II): Level 0 for scores 0–16 (euthymic); 1 for 17–22 (mild); 2 for 23–30 (moderate); and 3 for 31–63 (severe)[18].

Statistical analyses

Data-driven clustering analyses: A K-means clustering analysis was used for empirical subtyping. To optimize the data analyses, biological treatment history was longitudinally recorded for each participant in 4-wk intervals, yielding 24 sets of data points. Four parameters were used to capture the time-dependent prescription pattern for each class of psychotropic agents. In each participant, 24 data points for psychotropic load were calculated to determine the stability of prescribed dosage, frequency of high-dosage prescriptions, frequency of prescriptions, and the time trend of prescribed dosage. The stability of the prescribed dosage was a reflection of dosage fluctuation over the 2 year period. It was evaluated by estimating the coefficient of variance within the 24 points of data for each psychotropic load. Secondly, a count of high dosage prescriptions was obtained as an index of the need for high levels of specific interventions to achieve symptomatic control. The median of each class of psychotropic load was calculated for all participants using dichotomized cutoffs. The

24 data points for each class of psychotropic load in individual participants were compared with the cutoff. The total number of points in which the psychotropic loads were equal or greater than the median was recorded. Higher counts corresponded to a greater frequency of high-dosage prescription. Thirdly, the frequency of the prescription denoted the count of the presence of psychotropic load in the 24 data points. It represents the frequency of utilization of outpatient services and indicates the intensity of psychiatric care. Finally, the trend over time of the prescribed dosage evaluated the increments or decrements in psychotropic dosage. The correlation coefficient between each psychotropic load and time was determined for each participant to quantify the time trend of the prescribed dosage. A total of 12 parameters were generated for each participant. A K-means clustering analysis was performed using all collected parameters. The number of cluster K was an input parameter, and it was set at a priori between 3 and 5. The final class of subgroups was determined based on clinical relevance and implications. Additionally, we noted that if the scales of the input parameters are notably different, the contribution of these parameters may be uneven. Because the scales of 'the frequency of prescription' and 'the level of dosage' are greater than the other variables, we conducted sensitivity analysis to use these two parameters only, and perform the clustering analysis again. We then compared the differences of resultant clusters for evaluating the robustness of the current findings.

Between-cluster comparisons: After data-driven clustering analyses were completed using the K-means method, several clinical severity indicators were used to examine between-cluster differences. In these analyses, a Chi-square and analysis of variance (ANOVA) were used as univariate analyses. For multivariable regression analyses (excluding analyses of the severity of depression), all clinical severity data were taken into account, and Poisson regression analyses were conducted because of count data. General linear models were constructed in consideration of the between-cluster differences in depression severity at the end of the follow-up period. Data were analyzed using the SPSS version 17.0 (SPSS Inc., Chicago, IL, United States) statistical package. The statistical significance level was set at a P value of < 0.05.

RESULTS

A total of 105 individuals with first-onset MDD participated in the study. The average age of participants was 51.5 ± 13.2 years old, their age at MDD onset was 44.5 ± 13.6 years old, 75.5% were female, and 20.8% had concurrent anxiety disorders (Table 1).

According to the results of the K-means clustering analyses, 4 feature-based clusters were identified. Based on the differences between regimens, psychotropic load, and prescription duration, the clusters were designated as short-term antidepressant use (SA, n = 19), long-term antidepressant use (LA, n = 33), long-term antidepressants and sedatives use (LAS, n = 34), and long-term antidepressants, sedatives, and augmentation use (LASA, n = 19). The parameters used for the K-means clustering analyses are detailed in Supplementary Table 2. Additionally, SA and LA clusters were denoted as the simple pharmacy group, due to the relatively simple pattern of psychotropic agent use. In contrast, the LAS and the LASA clusters comprised the complex pharmacy group. Table 1 also summarizes the univariate comparisons of various demographic characteristics and clinical indicators between the 4 clusters.

Figure 1 depicts the change over time in the monthly equivalents in the 4 clusters based on three classes of psychotropic loads. The lowest average ADL for the first 2 years following disease onset in the SA reflects the lower initial dosage and shorter exposure period of these participants (Figure 1A). Figure 1A also demonstrates that ADL in the LA cluster is consistent over time and similar to the complex pharmacy group, while the dosage of antidepressants was lower in the LA cluster. This finding is consistent with a comparison of the averaged ADL values between clusters. Additionally, Figure 1B presents the time-course of SL in the 4 clusters. Complex pharmacy group clusters exhibited steady levels and the higher equivalent of hypnosedatives, which discriminates them from the simple pharmacy group. Figure 1C illustrates the unique properties of LASA in the prescription pattern of augmentation agents. The three clusters (excluding LASA) exhibited less monthly AUGL until 4 mo after MDD onset.

Table 2 summarizes the differences in various clinical severity indicators between clusters, after controlling for the confounding effects. In the first 2 years following MDD onset, no significant difference was observed between the 4 clusters in the numbers of antidepressants used. However, the number of ADAD in the SA was

Table 1 Univariate comparisons of demographic and clinical features by empirically-derived clusters (*n* = 105), mean ± SD

	Total	Simple pharmacy, short-term antidepressants use (SA, *n* = 19)	Simple pharmacy, long-term antidepressants use (LA, *n* = 33)	Complex pharmacy, long-term antidepressants and sedatives use (LAS, *n* = 34)	Complex pharmacy, long-term antidepressants, sedatives and augmentation use (LASA, *n* = 19)	*P* value for univariate omnibus test
Demographic and general clinical data						
Age (yr)	51.5 (13.2)	42.6 (14.4)	50.6 (15.2)	54.9 (9.1)	56.5 (10.3)	0.02
Age of onset (yr)	44.5 (13.6)	36.3 (14.4)	43.2 (15.3)	48.6 (10.0)	49.6 (11.0)	0.01
Female, *n* (%)	80 (75.5)	15 (78.9)	24 (72.7)	27 (79.4)	13 (68.4)	0.79
Comorbid anxiety disorder, *n* (%)	22 (20.8)	6 (31.6)	9 (27.3)	4 (11.8)	3 (15.8)	0.25
Number of comorbid physical diseases	0.7 (1.3)	0.5 (1.2)	0.7 (1.4)	1.1 (1.5)	0.6 (1.2)	0.39
Follow-up duration after 2-yr of disease onset (yr)	3.7 (3.5)	3.2 (3.2)	3.4 (3.1)	3.7 (3.2)	3.8 (3.9)	0.91
Psychotropic loads						
Antidepressant load (defined daily dose/month)	34.5 (18.4)	13.3 (7.2)	32.1 (13.1)	42.8 (17.3)	44.8 (17.7)	< 0.001
Sedative load (equivalent dose/month)	57.3 (56.8)	8.1 (10.8)	18.5 (20.9)	91.9 (45.4)	112.0 (56.7)	< 0.001
Augmentation load (defined daily dose/month)	1.2 (2.7)	0.1 (0.5)	0.3 (0.6)	0.3 (1.0)	5.3 (4.0)	< 0.001
Clinical feature within 2-yr of disease onset						
Number of antidepressants use	1.7 (0.9)	1.3 (0.6)	1.6 (0.8)	1.9 (1.1)	1.9 (0.9)	0.07
Number of antidepressants use with adequate dosage and duration	1.5 (0.9)	1.1 (0.5)	1.3 (0.8)	1.7 (1.2)	1.8 (0.8)	0.04
Visits of psychiatric outpatient service	17.3 (10.7)	10.6 (5.8)	15.5 (5.1)	20.2 (10.6)	21.8 (17.1)	0.002
Frequencies of psychiatric admission	0.2 (0.5)	0.1 (0.3)	0.2 (0.4)	0.1 (0.3)	0.7 (0.8)	< 0.001
Clinical feature beyond 2-yr of disease onset						
Visits of psychiatric outpatient service	31.1 (66.7)	9.7 (10.3)	20.2 (24.7)	41.4 (91.6)	42.6 (78.4)	0.22
Frequencies of psychiatric admission	0.8 (0.5)	0.0 (0.0)	0.1 (0.4)	0.1 (0.7)	0.0 (0.0)	0.71
Severity of depression in the recruitment[1]	1.5 (0.9)	0.6 (1.0)	0.9 (1.2)	1.2 (1.3)	1.7 (1.2)	0.02

[1]Severity of depression was scored according to the level of depression, which was evaluated by the Beck Depression Inventory.

significantly lower than in LAS (P = 0.04) and LASA (P = 0.03). Although the average ADL of LA is significantly lower than the complex pharmacy group (Table 1), the number of used antidepressants and ADAD did not significantly differ between the LA and the complex pharmacy group clusters. Analysis of the use of outpatient services within the first 2 years of disease course, showed a significantly lower number

Table 2 Multivariable analyses for the comparisons of clinical features by empirically-derived clusters (*n* = 105)

	Simple pharmacy, short-term antidepressants use (SA, *n* = 19)	Simple pharmacy, long-term antidepressants use (LA, *n* = 33)	Complex pharmacy, long-term antidepressants and sedatives use (LAS, *n* = 34)	Complex pharmacy, long-term antidepressants, sedatives and augmentation use (LASA, *n* = 19)	*P* value for pos-hoc comparison using multivariable regression test
	IRR (95%CI)	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	
Clinical feature within 2-yr of disease onset[1]					
Number of antidepressants use	0.57 (0.32-0.82)	0.74 (0.52-0.97)	0.94 (0.66-1.23)	0.96 (0.61-1.31)	
Number of antidepressants use with adequate dosage and duration	0.50 (0.26-0.73)	0.64 (0.44-0.85)	0.87 (0.59-1.15)	0.95 (0.60-1.31)	SA < LAS (P = 0.04); SA < LASA (P = 0.03)
Visits of psychiatric outpatient service	4.76 (4.04-5.47)	7.46 (6.75-8.17)	10.34 (9.37-11.30)	11.37 (10.15-12.58)	SA < LA (P < 0.001); SA < LAS (P < 0.001); SA < LASA (P < 0.001); LA < LAS (P < 0.001); LA < LASA (P < 0.001)
Frequencies of psychiatric admission	0.03 (-0.02-0.08)	0.05 (-0.002-0.10)	0.03 (-0.01-0.08)	0.24 (0.04-0.44)	SA < LASA (P = 0.01); LA < LASA (P = 0.004); LAS < LASA (P = 0.001)
Clinical feature beyond 2-yr of disease onset					
Visits of psychiatric outpatient service[2]	3.03 (2.58-3.49)	5.81 (5.34-6.30)	10.21 (9.49-10.93)	10.86 (9.98-11.74)	SA < LAS (P < 0.001); SA < LA (P < 0.001); SA < LASA (P < 0.001); LA < LAS (P < 0.001); LA < LASA (P < 0.001)
Frequencies of psychiatric admission[3]	-	-	-	-	
	EMM (95%CI)	**EMM (95%CI)**	**EMM (95%CI)**	**EMM (95%CI)**	
Severity of depression in the recruitment[4]	0.58 (0.23-0.93)	0.90 (0.54-1.25)	1.66 (1.10-2.22)	2.20 (1.37-3.30)	SA < LAS (P = 0.002); SA < LASA (P < 0.001); LA < LAS (P = 0.02); LA < LASA (P = 0.001)

[1]Covariates included into the Poisson regression model were sex, age of onset, comorbid anxiety disorder, and number of medical comorbidities. OFFSET = logarithm (2).
[2]Covariates included into the multivariable Poisson regression model were sex, age of onset, comorbid anxiety disorder, and number of medical comorbidities. OFFSET = logarithm (duration of course beyond 2-yr of disease onset).
[3]Covariates included into the multivariable Poisson regression model were sex, age of onset, comorbid anxiety disorder, and number of medical comorbidities. OFFSET = logarithm (duration of course beyond 2-yr of disease onset). This model failed to converge because of zero count in some clusters.
[4]Covariates included into the general linear model were sex, age of onset, comorbid anxiety disorder, number of medical comorbidities, and duration of course beyond 2-yr of disease onset. Severity of depression was scored according to the level of depression, which was evaluated by the Beck Depression Inventory. IRR: Incident rate ratio; EMM: Estimated marginal mean.
CI: Confidence interval.

of visits in the clusters of the simple pharmacy group compared with those in the complex pharmacy group. Furthermore, LA exhibited greater visits to the outpatient services than SA (P < 0.001), but no significant difference was observed between the LAS and the LASA. The LASA cluster exhibited a higher frequency of psychiatric admission in the first 2 years after MDD onset, compared with the other 3 clusters. However, SA, LA, and LAS did not differ in terms of admission frequency. The simple pharmacy group exhibited a lower frequency of visits to outpatient services after 2 years from disease onset than the complex pharmacy group. However, no significant difference was observed between LAS and LASA. Finally, the clusters in the complex pharmacy group exhibited more severe depressive symptoms than the clusters of the simple pharmacy group. However, no within-group differences were found in terms of depression severity in both the simple and complex pharmacy groups (Table 2).

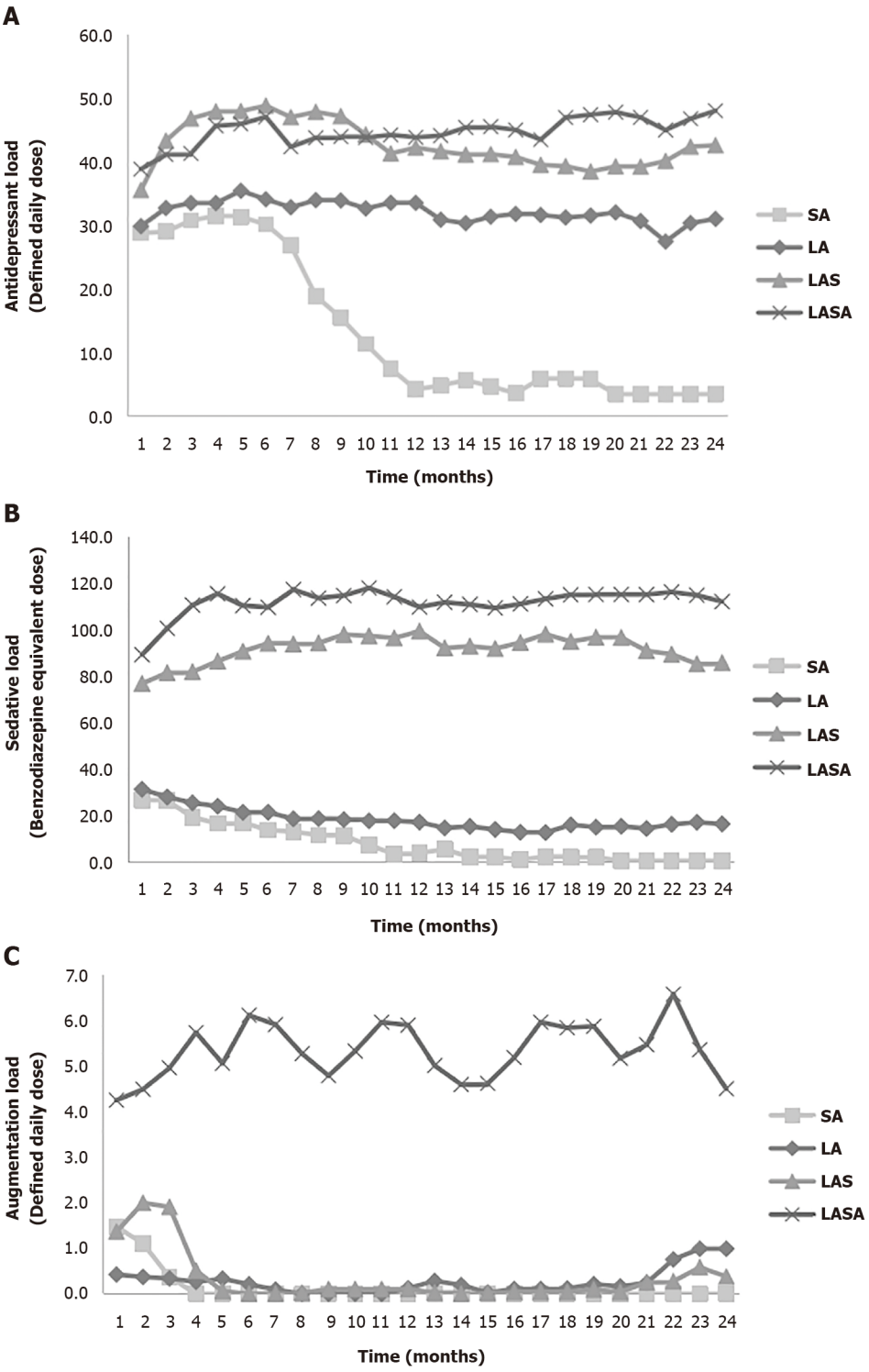


Figure 1 The trends of psychotropics use after the onset of major depressive disorder, illustrated by feature-based clusters. A: Antidepressant loads; B: Sedative load; C: Augmentation loads. LA: long-term antidepressants use; LAS: Long-term antidepressants and sedatives use; LASA: Long-term antidepressants, sedatives and augmentation use; SA: Short-term antidepressants use.

To evaluate the robustness of the clustering results, we re-analyzed the data with various parameter combinations. Our sensitivity analysis revealed similar clustering results. By adopting only 2 parameters, the frequency of high-dosage prescriptions, and the frequency of prescriptions, the K-means clustering analysis still yielded the same 4 clusters as were generated by the original 4 parameters.

DISCUSSION

The patients were empirically classified into 4 clusters according to the K-means clustering analysis that dissected the time-dependent prescription pattern over the first 2 years following the onset of the first episode of MDD. This analysis was facilitated by novel parameters that successfully capture the reciprocal interactions between physicians' prescriptions and disease status in a real-world setting. The 4 identified clusters exhibited distinct patterns in terms of the dosage of psychotropic agents, duration of prescription, and the combinations of psychotropic agents used. Additionally, the 4 clusters also exhibited differences in severity of clinical indicators. To the best of our knowledge, this is the first attempt to classify MDD by pharmacological dissection considering time-dependent prescription patterns using a data-driven clustering analysis.

While no between-cluster differences were observed in the number of antidepressants used in this study, the SA exhibited lower number of ADAD used, compared to the clusters comprising the complex pharmacy group. In the clinical setting, the number of antidepressants used reflects the expense involved in the use of sequential trials to select appropriate antidepressants. In contrast, the number of ADAD is a reflection of inadequate treatment response after a series of interventions[19]. Therefore, data-driven clusters in the present study suggest a different level of treatment difficulty, beyond the number of trials used to identify a tolerable antidepressant regimen. Furthermore, the use of psychiatric facility (an index of clinical disease burden) showed differences between clusters. The complex pharmacy group exhibited higher number of visits to outpatient services compared to the simple pharmacy group within the first 2 years following MDD onset and beyond. The use of outpatient services reflects the need for re-evaluation or stabilization of symptoms, and serves as an indicator of long-term treatment stability. Taken together, our findings suggest that the patients in the complex pharmacy group require more intensive care to stabilize their symptoms. Similarly, the level of BDI-II-defined depression on the recruitment day corresponded to the pattern of residual symptoms over time in the complex pharmacy group. Finally, psychiatric admissions are often indicated in life-threatening conditions or situations where the treatment response remains inadequate after a series of guideline-based interventions. LASA, in comparison with other clusters with low AUGL, uniquely exhibited a highest frequency of psychiatric admissions. These findings support the clinical relevance of the prescription-based subtyping strategy.

According to the established pharmacological mechanisms of each class of psychotropic agent, the four prescription-based clusters correspond to distinct biological mechanisms. In the simple pharmacy group, SA and LA were associated with similar initial doses of antidepressants, but differed in the duration of prescription. Consistent with the clinical practice, the episodes in the SA cluster exhibited the expected response to antidepressants during the acute and maintenance phases. In contrast, LA cluster of patients needed a longer period of maintenance therapy due to vulnerability to relapse or recurrence, despite the apparent adequate antidepressant treatment. This finding suggests that the traditional monoaminergic antidepressants can correct the neurochemical deficits of MDD in clusters comprising the simple pharmacy group.

Compared with the relatively short-term and low-dose exposure to hypnosedatives in the simple pharmacy group, clusters in the complex pharmacy group were characterized by longer duration and high doses of hypnosedative use. Interestingly, the rate of comorbidity of anxiety disorders did not differ significantly between the 4 clusters. Although antidepressants were suggested as the primary therapy for anxiety[20], monoaminergic antidepressants alone seem insufficient for patients in the complex pharmacy group. Contrary to the recommendation of short-term adjunct use of hypnosedatives in the treatment guidelines[21], depending on study populations, 7.6 to 60% patients with MDD initiated antidepressant treatment with concurrent hypnosedatives, while 12% to 48% of patients received long-term combined treatment [22-28]. Indeed, the monoaminergic deficiency hypothesis was regarded as insufficient to explain the heterogeneity of MDD[29]. Additionally, monoaminergic antidepressants and benzodiazepines may alleviate the anxiety symptoms through different mechanisms[29,30]. Therefore, clusters within the complex pharmacy group may have specific pathogenic mechanisms that cannot be resolved by monoaminergic antidepressants alone, such as deficits in the gamma-aminobutyric acid-related system[29]. This finding suggests that, instead of subgrouping by comorbidity of anxiety disorders, classifying individuals by hypnosedative use pattern over 2 years may be more informative and facilitate the identification of common neurochemical deficits among these patients. Moreover, in addition to long-term hypnosedative use, LASA is

characterized by long-term concomitant use of augmentation agents. Because various medications with different pharmacological mechanisms were included as augmentation agents in this study, the heterogeneity of neurochemical deficits in the LASA cluster may be more complex than originally believed.

Clusters comprising the complex pharmacy group exhibited a higher initial SL that persisted over the first 2 year after MDD onset. This is consistent with the previously published findings showing that depressed patients who used a higher daily dosage of sedatives in the initial treatment phase tend to be long-term users[28]. Additionally, the association between sedative use and clinical severity was previously found to be independent of the use of antidepressants and augmentation agents[10]. The complex pharmacy group in this study exhibited high dosage and long duration of hypnosedatives use, which correlated with worse indicators of disease severity. However, when AUGL is taken into account, participants with long-term use of hypnosedatives could be further partitioned into LAS and LASA, which differ in aspects of clinical severity (Table 2). In this study, the time-dependent pattern of ADL separated the SA, LA, and clusters comprising the complex pharmacy. When SL and AUGL are taken into consideration, a difference was detected between clusters, enhancing the clinical implications of these data-driven clusters. Therefore, simultaneous inclusion of the 3 classes of psychotropic loads has distinct and complementary function in the clustering analysis.

There are a number of limitations to this study. First, the strict inclusion criteria resulted in a sample size which is not large enough to ensure that all statistical models are sufficiently powered. However, under the current sample size, most of the analyses have successfully demonstrated between-cluster differences in terms of clinical severity indicators. This observation indirectly supports a significant extent of between-cluster differences between the resulting clusters. Additionally, people in Taiwan have high accessibility and availability to medical resources. Since eligible participants had to have at least 2 years of complete treatment history in a teaching hospital, they usually exhibited superb adherence, which may influence the selection of participants. Therefore, study findings may not be generalized to all patient groups. Second, medications compliance is unknown in our participants. Therefore, the presented psychotropic loads may not reflect the actual dose taken by the participants. Moreover, we did not know if the patients concurrently received pharmacological or non-pharmacological treatment from other hospitals, which could introduce misclassification bias. Third, baseline severity of depression was not evaluated in this study. However, findings of a previous study suggest that the initial severity of MDD is not correlated with treatment response[31]. Absence of this information is unlikely to change the clustering results. Fourth, the latency from the disease onset to the commencement of treatment is not recorded in this study. Since the delay in treatment makes it more difficulty to treat the major depressive episode, this may introduce bias in inference of homogeneity in pathogenic mechanisms between clusters. Finally, the resultant clusters in this study may merely reflect therapists' prescription preferences. According to the examination of clinical validity, we believe that these empirically-derived clusters, at least in part, reflect the underlying pathological mechanisms.

CONCLUSION

With the trend of increased data sharing of medical registries, prescription patterns are well established in most data banks. While claimed based datasets do not have detailed information on symptoms or dynamic disease status in a real-world setting, these kinds of data would have large sample size and large amounts of data regarding prescription patterns. By using such kinds of databases, researchers not only can investigate the heterogeneity of MDD but also explore the complexity feature with other comorbid health conditions, and can easily expand to study other mental disorders. Additionally, machine learning approaches, such as K-means clustering analyses can be used to optimize the subgrouping information. In the future, this technique can be enhanced by reducing the required number of input parameters and duration of prescription records. The biological validity, generalizability, and predictive value of this new clustering approach warrant further investigation.

ARTICLE HIGHLIGHTS

Research background

Major depressive disorder (MDD) is a common and challenging mental illness. Even though research on the biological substrates of MDD is increasing, the heterogeneity of MDD substantially compromises the applicability of these study findings. Thus, subgrouping MDD into homogeneous clusters, which could be used to investigate specific neurobiological and pathological mechanisms, is a promising solution.

Research motivation

The heterogeneity in MDD is derived from multiple aspects of the disease. There is inadequate evidence to support the existence of symptom-based subtypes. Thus, we intended to develop a novel approach by clustering patients with similar biologically relevant potentials.

Research objectives

We aimed to develop a novel approach to tackle the heterogeneity in drug-naive patients experiencing their first episode of MDD, using detailed prescription patterns of major psychotropic classes during the early disease course.

Research methods

Psychotropic agents prescribed in the first 24 mo following disease onset were recorded monthly and categorized as antidepressants, augmentation agents, and hypnosedatives. Four parameters were used to summarize the time-dependent prescription patterns for each psychotropic agent. A K-means cluster analysis was used to derive subgroups of participants based on these four parameters of psychotropic agents across 24 mo.

Research results

The patients were empirically classified into 4 clusters according to the K-means clustering analysis that dissected the time-dependent prescription pattern over the first 2 years following the onset of the first episode of MDD. The four identified clusters exhibited distinct patterns in terms of the dosage of psychotropic agents, duration of prescription, and the combinations of psychotropic agents used. Additionally, the four clusters also exhibited differences in severity of clinical indicators.

Research conclusions

Our novel parameters successfully captured the reciprocal interaction between physicians' prescriptions and disease status in a real-world setting. This study presents a novel clustering strategy that can be used to generate prescription-based subtypes.

Research perspectives

Machine learning approaches, such as K-means clustering analyses can be used to optimize the subgrouping information. The biological validity, generalizability, and predictive value of this new clustering approach warrant further investigation.

ACKNOWLEDGEMENTS

The authors would like to thank the Dr. Chin-Hao Chang for the assistance of statistical analysis; Dr. Chih-Kang Hsu, Dr. Hsien-hsueh Shih, Dr. Yen-Chin Wang, Dr. Hai-Ti Lin, Dr. Tzu-Yu Liu, Dr. Meng-Shiuan Shie and research assistants Miss I-Chen Huang and Miss Chieh-Chun Hu for their help with data collection.

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World J Psychiatr 2021 November 19; 11(11): 1129-1146

DOI: 10.5498/wjp.v11.i11.1129

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

New-onset depression after hip fracture surgery among older patients: Effects on associated clinical outcomes and what can we do?

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Author contributions: Qin HC and Luo ZW conducted the original search and wrote the first draft of the paper; Qin HC, Luo ZW ,and Chou HY screened the selected articles and contributed to subsequent drafts of the manuscript; Zhu YL conceived the idea for the study and provided suggestions; Qin HC and Luo ZW made equal contributions to the work.

Conflict-of-interest statement: The authors admitted that there is no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific

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Abstract

BACKGROUND

Hip fracture in the elderly is a worldwide medical problem. New-onset depression after hip fracture has also received attention because of its increasing incidence and negative impact on recovery.

AIM

To provide a synthesis of the literature addressing two very important questions arising from postoperative hip fracture depression (PHFD) research: the risk factors and associated clinical outcomes of PHFD, and the optimal options for intervention in PHFD.

METHODS

We searched the PubMed, Web of Science, EMBASE, and PsycINFO databases for English papers published from 2000 to 2021.

RESULTS

Our results showed that PHFD may result in poor clinical outcomes, such as poor physical function and more medical support. In addition, the risk factors for PHFD were summarized, which made it possible to assess patients preoperatively. Moreover, our work preliminarily suggested that comprehensive care may be the optimal treatment option for PHFDs, while interdisciplinary intervention can also be clinically useful.

quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: May 17, 2021
Peer-review started: May 17, 2021
First decision: June 23, 2021
Revised: June 25, 2021
Accepted: August 23, 2021
Article in press: August 23, 2021
Published online: November 19, 2021

P-Reviewer: Wang W
S-Editor: Yan JP
L-Editor: Filipodia
P-Editor: Guo X

CONCLUSION
We suggest that clinicians should assess risk factors for PHFDs preoperatively, and future research should further validate current treatment methods in more countries and regions and explore more advanced solutions.

Key Words: Depression; Hip fracture; New onset; Risk factors; Treatments; Clinical outcomes

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Core Tip: Although postoperative hip fracture depression (PHFD) has terrible effects on older patients, the risk factors, associated clinical outcomes, and treatments have not been systematically summarized. The comprehensive identification of risk factors is clinically useful in preoperative assessment and early prevention of PHFD. In addition, the summarized treatment options for PHFDs can suggest what circumstances treatment works best, providing a credible guide for effective management for clinicians.

Citation: Qin HC, Luo ZW, Chou HY, Zhu YL. New-onset depression after hip fracture surgery among older patients: Effects on associated clinical outcomes and what can we do? *World J Psychiatr* 2021; 11(11): 1129-1146
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1129.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1129

INTRODUCTION

Hip fractures are one of the most common physical injuries in the elderly, and they often occur after a sudden fall in older people with osteoporosis. In addition to osteoporosis, other risk factors include aging, osteoarthritis, malnutrition, muscle weakness, arthritis, and visual impairment[1-3]. At least 120 million people around the world are affected by hip fractures. Between 2012 and 2016, the cumulative incidence of hip fractures among those aged 55 years and over in urban China was 148.75 per 100,000. Moreover, the cost of hospitalization for hip fractures increased six-fold from 2012 to 2016, while per person, it increased by 1.59 times[4,5]. Given that the global population of the middle-aged and elderly is expanding, hip fractures will be sure to transform into a significant challenge and a critical health issue for all of humanity. The 1 mo mortality rate after hip fracture surgery is approximately 5% to 8%[6], while the cumulative mortality rate at 12 mo is 33%[7]. In addition to the high mortality rate, hip fractures threaten patients' functional status in all aspects[8,9], especially ambulation ability in the elderly[10]. Even among those who lived in the community before their hip fracture, 11% ended up as bedridden, 20% did not regain normal walking ability, fewer than 30% returned to their previous level of activity, and 80% used walking aids for a year after their hip fracture[1,11].

Depressive symptoms are also prevalent among the old[12], and the onset of depression is obviously associated with a sudden injury or illness that can lead to hospitalization. This is also how postoperative hip fracture depression (PHFD) occurs. Wilson *et al*[13] also defined this as new-onset depression, a postoperative diagnosed disease following a depression-free preoperative period, which has been well described in certain cohorts. The prevalence of depressive symptoms is up to 50% among hospitalized older adults, and over one-third of the sample in the study by Ciro *et al*[14] reported high depressive symptoms during hospitalization. The incidence of depression is also high in patients with broken hips[15]. Information extracted from multiple studies[16-19] showed that the prevalence of depression after hip fracture ranged from 9% to 47%. In the systematic review and meta-analysis by Heidari *et al*[20], researchers concluded that the prevalence of depression among older hip fracture patients was 23% (95% confidence interval [CI]: 0.18–0.29). Many studies have proven that older adults with depression are associated with emotional suffering, rising health expenditures, higher risk of suicide, and diminishing quality of life (QOL)[21-23]. There is a clinical association between hip fracture and depression. Loss of walking

ability, poor QOL, pain, and a sense of loss of future life caused by hip fracture are potential risk factors for depression.

This review explores the risk factors related to PHFD, its adverse clinical outcomes, and effective interventions by means of a literature search. It is expected to provide ideas for clinical workers to deal with the disease and provide direction for researchers.

MATERIALS AND METHODS

We referred to previously published literature search methods[24]. We used the PubMed, Web Of Science, EMBASE, and PsyclNFO databases to conduct a systematic review of the published literature and searched up until December 31, 2020. The search terms were hip fracture, femoral neck fracture or femoral intertrochanteric fracture and depression, and depressive disorder or low mood (search strategy, Figure 1). We researched reference lists of previously published reviews and studies in these reviews to ensure that no papers were missed. There were no restrictions on language or country of publication. After removing the same study from different databases, two reviewers (Qin HC, Luo ZW) assessed the titles and abstracts of initial papers independently and determined the final inclusion eligibility. Then either reviewer identified the full text of all possibly relevant records and included all subtypes of PHFD. Differences were settled by consensus (Figure 2).

RESULTS

How does PHFD develop (pathogenesis of PHFD)?

From the micro point of view regarding the formation of postoperative depression, postoperative peripheral inflammation can lead to an increase in proinflammatory cytokines in the brain in various ways, resulting in cognitive impairment[25]. In turn, these inflammatory factors continue to affect structures in the brain such as glia (microglia and astrocytes), the neurotrophic support of neurons, and changes in the cytotoxicity of neurons.

Looking at this from a macro perspective, the changes in all aspects of life brought about by a hip fracture operation have varying degrees of psychological impact. These include the fear of becoming too dependent on caregivers and placing too much burden on family members; fear that the body will not be able to function as before; loss of hope, confidence, or anxiety about future life; feeling lonely and isolated because their daily activities are restricted; and fear of falling again or even death. These psychological changes after surgery all contribute to the formation of depressive symptoms to a certain extent.

Risk of developing depression in hip fracture

In patients with PHFDs, there are many risk factors that contribute to the progression of the disease including age, sex, complications, types of fracture and preoperative status, and emotional-social support. With a thorough understanding of its risk factors, we can efficiently prevent and diagnose the disease in a timely manner.

Age and frailty: Epidemic data show the link between age and hip fractures; the number of hip fractures and the cost of treatment are increasing in China due to the aging of the population. In the study by Cheng *et al*[26], there were statistically significant differences in the incidence of hip fractures among different age groups. Meanwhile, as people grow older, loss of bone and muscle mass increases the risk of falling, leading to fractures[27]. Age is also an important factor in the development of depression. Both the prevalence and the incidence of major depression double after the ages of 70–85[28]. Combining these two factors, age as a risk factor for both hip fracture and depression, suggests that age is a potential risk factor for the development of PHFD. Williams *et al*[29] discovered that the odds ratios (ORs) for depression following fractures among younger women (≤ 65 years) were 0.62 (0.35 to 1.11; P = 0.12) and 3.33 (1.24 to 8.98; P = 0.02) for older women (> 65 years). However, new knowledge is emerging that frailty, an age-related cumulative decline in multiple physiological systems, is a better predictor of mortality and morbidity than chronological age[30]. At the same time, many of the items in the assessment of frailty are risk factors for fractures and depression[31]. The identification and assessment of frailty

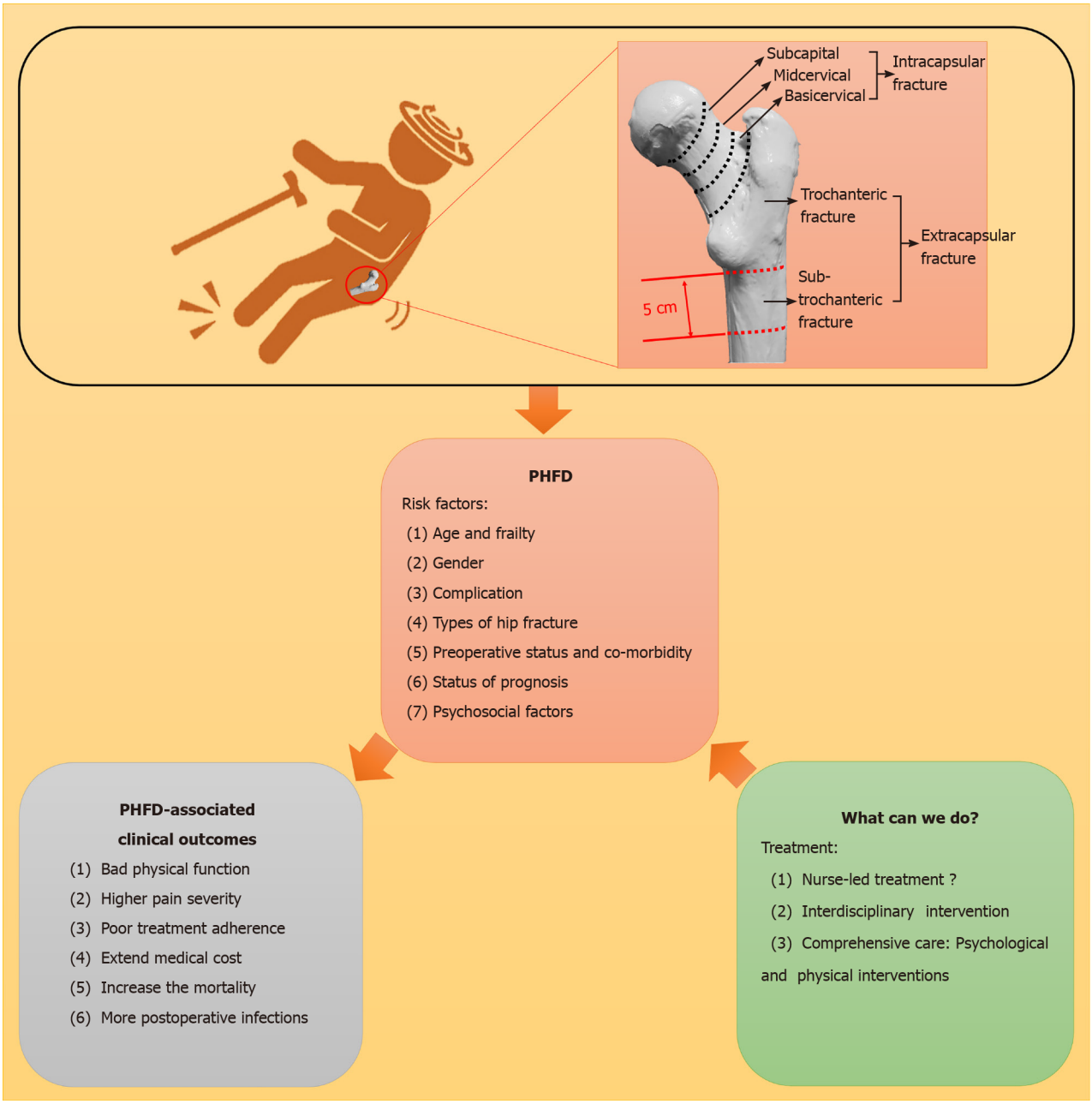


Figure 1 The full-text summary diagram. PHFD: Postoperative hip fracture depression.

may facilitate the identification of vulnerable preoperative patients so that management can be implemented in a timely manner. The association between the frailty index (as a risk factor) and the risk of PHFD is still unknown, and subsequent research is required to prove this association.

Sex: Among several factors that can influence the epidemiology of hip fractures, sex seems to be the most relevant factor. According to epidemiological data on depression in older adults, depression affects twice as many women as men[28]. Hip fracture is an important and debilitating condition in older people, especially women. Epidemiological data vary between countries, but it is globally estimated that hip fractures will have an influence on approximately 18% of women and 6% of men[8]. An essential reason is that functional outcomes reported between males and females in survivors and functional outcomes between men and women are most often reported as equivalent or favoring men, although men are consistently reported as having more postoperative complications[32]. For example, at discharge, men were more independent in locomotion, transfers, and sphincter control[33]. It is also possible that the difference is artificial and that sex differences in help-seeking behavior or symptom reporting exist to the extent that women are more likely to admit and complain about

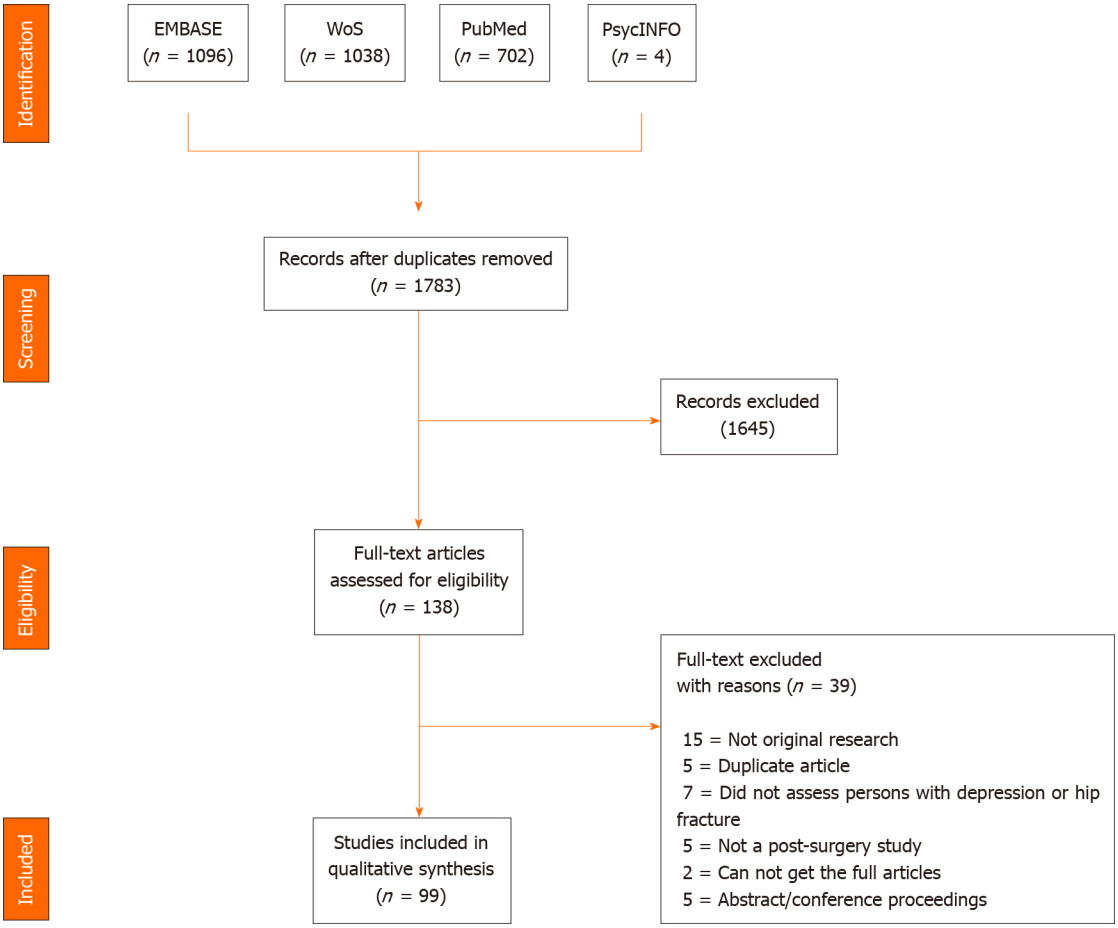


Figure 2 Flowchart diagram of the electronic search.

their dysphoric feelings than men, who are more likely to deny and instead of act them out[34]. However, there is some controversy. For example, although the incidence is higher in women than in men, the severity of postoperative depression in men is often higher than in women, and the ratio of men to women varies by type of depression [35].

Types of hip fracture: Surgical treatment of hip fractures is mainly divided into internal fixation, hemiarthroplasty, and total arthroplasty. Studies have shown that sex and age are associated with different hip fractures[36]. Extracapsular-intertrochanteric fractures were found to increase dramatically with age in women. Since sex and age are risk factors for the development of PHFDs, the type of fracture also plays an important role. Moreover, the postoperative status and rehabilitation requirements for all kinds of T fractures vary, thus representing the differences in the recovery of patients' postoperative activity ability, which has become one of the leading factors for the development of PHFDs. Elderly patients who receive internal fixation surgery for femoral intertrochanteric fracture do not recommend weight bearing of the affected hip joint at an early time of recovery. A considerable number of patients are still in bed or sitting in a chair for a long time within 1 mo after discharge. Therefore, displaced femoral neck fractures, treated with total hip arthroplasty or hemiarthroplasty, provide a better functional outcome than treatment with internal fixation[37].

Preoperative status and comorbidity: The preoperative status determines the maximum degree of recovery from surgery to some extent. In the study by Shyu *et al* [38], the authors found that those who were female and had lower prefracture activities of daily living performance were more likely to be at higher risk for depression. Poor nutritional status can also induce postoperative pain[39]. In addition to poor motor function and nutritional status being risk factors for the development of PHFDs, some articles found that chronic preoperative opioid use, history of smoking, drug or alcohol use disorder, and preoperative smoking were also risk factors[13,40]. Patients with underlying conditions are often more vulnerable to another condition.

The presence of comorbidities such as preoperative anxiety disorder[13], cardiovascular disease, diabetes, and cognitive dysfunction was associated with the incidence of postoperative depression[41]. In Miguel-Diez *et al*[42], the authors concluded that the incidence of hip fracture is higher in subjects with chronic obstructive pulmonary disease. Liu *et al*[43] discovered that predisposed patients with fewer comorbidities belong to the progressively lower-risk group rather than the fluctuating higher-risk group, which suggests that more comorbidities increase the risk of long-term depression following hip fracture. Unfortunately, after extensive literature research, no scale can be found to quantify the association between PHFD and preoperative comorbidities. Given that this may provide better risk stratification, this scale should be created in subsequent studies.

Status of prognosis: The quality of prognosis can be divided into acute and long-term outcomes, and both are sure to be risk factors accelerating depression. In the prognosis of the acute phase, pain is an important risk factor for PHFD. Numerous articles[44-46] have examined the mechanisms linking pain and depression, indicating that pain can remodel neural pathways to trigger negative symptoms of depression. Voshaar *et al* [15] identified postoperative pain and baseline anxiety as the strongest independent risk factors for depression. Bruggemann *et al*[47] provides tentative evidence that postinjury beliefs and hopelessness influence levels of depression and anxiety in hip fracture patients in the acute phase of their injury. Long-term risk factors such as loss of walking ability and reduced self-care ability can contribute to the progression of depression. Studies have also indicated a significant difference in the incidence of depression between homebound and semi-homebound elderly adults[48]. The psychological changes of the patient as they recover are also important[49]. Prolonged bedtime, reduced range of activity, and severe effects on the ability to perform daily activities are all susceptible to forming a sense of helplessness. In conclusion, each stage of the patient's psychological and physical changes after surgery can affect the development of depression.

Psychosocial factors: Patients' education, which is often overlooked, is linked to depression. In Liu *et al*[43], researchers distinguished groups of postoperative depressive-symptom trajectories, and found that patients in the progressively lower-risk group were less likely to be illiterate than those in the fluctuating higher-risk group (P = 0.02). Emotional support from family, friends, and society plays an important role in one's psychological development, especially those who have experienced impaired health-related QOL[50]. Low socioeconomic status[51], living in a rural area, being unmarried, and housing circumstances promote depression disorder, although no direct experimental data have demonstrated an association between PHFD and these factors.

PHFD-associated clinical outcomes

Depression alone or hip fracture alone can lead to a decrease in QOL. The purpose of this part is to summarize the serious clinical outcomes of PHFDs. Exploring the impact of PHFDs on patients can help doctors provide more comprehensive treatment strategies.

PHFD has a great impact on physical function. There was a unanimous conclusion that during the first months after a hip fracture, the physical functioning of all the patients was seriously affected. At the same time, depression symptoms were associated with worse patient-reported outcomes[9,52,53]. The trial by Kohring *et al* [54] quantified the effect of depression on physical function recovery; untreated depressed patients demonstrated significantly smaller gains in physical function computerized adaptive test scores than nondepressed patients. The changes in preoperative and postoperative adjusted mean scores ranged from 37.8 to 45.1 in the nondepression group compared to 38.3 to 45.1 in the untreated depression group (P = 0.020). These results suggest that the recovery of physical function in patients with postoperative depression is very limited. Moreover, Gialanella *et al*[55] found that neuropsychiatric symptoms made the rehabilitation process slower and less efficient in hip fracture patients. The decline in physical function is bound to affect the QOL, in turn affecting the patient's psychological changes. Therefore, it is necessary to put an end to this vicious cycle.

Affect postoperative physiological and psychological reactions: Some experiments have reported a statistically significant effect of depression on postoperative pain, resulting in aggravation of both conditions[56,57]. Afton *et al*[58] found that

improvements in depression and anxiety symptoms after surgery were associated with enhancements in pain severity and physical dysfunction. In Cristancho *et al*[59], researchers found that a group experiencing a persistently high level of depressive symptoms had poorer functional recovery and higher rates of pain in the year following hip fracture. However, there are new experimental data[60] showing that the relationship between pain and the geriatric depression scale (GDS) after hip fracture is not statistically significant. The effect of depression on postoperative pain needs to be further determined. In addition to causing pain, depression triggers complications after surgery. The analysis by Pan *et al*[61] of the relationship between psychiatric disorders and postoperative outcomes in patients undergoing primary total knee arthroplasty showed that patients with psychiatric disorders had higher ORs for most complications. Second fracture, rate of intensive care unit inpatient[62], postoperative infections[63], and chronic medical illness[64] are all linked to depression. In terms of psychological reaction, patients often show poor adherence, cognitive impairment[65], and poor motivation, which directly affect the rehabilitation and medication process.

More medical support is required: Sullivan *et al*[66] found that depression was significantly correlated with longer hospital longer limits of stability (LOS) while controlling for demographics and injury severity (P = 0.023) by looking at 460 subjects. Longer hospital stays[67] mean increased health care costs and a reduced flow of inpatients. Shelley *et al*[57] also statistically analyzed the relationship between injury- and hospital-related variables and posttraumatic stress disorder and depression at baseline and 12 mo after orthopedic trauma, showing that depression at baseline and 12 mo was associated with mechanical ventilation and LOS. In addition, the cost of treating a variety of complications mentioned in the previous section associated with postoperative depression accounts for a large part of the cost. Given increasing health care costs and the condition in which hospital beds are scarce, it is necessary to reduce the incidence of postoperative depression as much as possible to alleviate this situation.

Increase the possibility of rehospitalization: Gold *et al*[68] showed that overall, 90-d readmission rates were approximately 8% for total hip arthroplasty (THA) and total knee arthroplasty (TKA), while the readmission for subjects with depression was 21%-24% higher overall. Therefore, depression is related to a markedly higher risk of readmission after THA and TKA. Reduced readmissions can facilitate the rationalization of the allocation of medical resources and exert apparent impacts on cost and quality. Hospital readmission rates are increasingly used as an indicator of health care quality and a potential source of regulatory penalties for hospitals[69]. At present, there are few studies on the direct effect of PHFDs on readmission, and further studies are needed.

Hip fracture is a common cause of mortality in older adults[70] and has a 1-year mortality of approximately 25%[71]. Older people with depression also have a higher mortality than average[28]. Both factors were independent predictors of mortality in elderly individuals. Liu *et al*[72] listed the risk factors for mortality in elderly patients with hip fractures, and depression was included. Nightingale *et al*[73] concluded that depressive symptoms increase the risk of mortality in patients with hip fracture in the following 2 years. By contrast, Hershkovitz *et al*[74] demonstrated that only dementia and age were independent predictors of mortality in hip fracture patients during the first 2 years after discharge from a post-acute rehabilitation program, while the presence of depression was not. As the most important clinical concern, patient mortality should be given sufficient attention.

Why does PHFD have such clinical outcomes? Patients with depression may feel hopeless, lack motivation, and be apathetic predisposing them to not participate actively in rehabilitation (adverse effects of depression and cognitive impairment on rehabilitation participation and recovery from hip fracture)[75]. Therefore, depression may exert its negative effect as a mediator *via* differential response to rehabilitation as well as other behaviour with a potential negative effect such as decreased activity, decreased social behaviour, and impaired diet.

Duggal *et al*[16,76-78] performed a series of studies and found that neutrophil bactericidal properties, monocyte and natural killer cell functioning, and T regulatory immune cells were impaired only in hip fracture patients who developed depressive symptoms. The dysregulation of these immune cells lead to a decline in immune system function and easily lead to postoperative infection.

People with depression tend to have higher cortisol levels than normal people. The higher the cortisol levels in older people, the frailer they are and the worse their physical function[79]. Low levels of serum anti-glucocorticoid dehydroepiandrosterone (DHEAS) sulfate have been associated with poorer physical function. Phillips *et al*[18] found that the ratio of cortisol to DHEAS was significantly higher in patients with PHFDs and was also associated with poorer physical function. The effects of depression on physical functioning may also be mediated by regulating these two substances.

DISCUSSION

Interventions for PHFD

To prevent the negative effects of depression on postoperative recovery and allow patients to recover to the preoperative physical condition as much as possible with less time, effort and cost, PHFD intervention is necessary. The interventions, inclusion criteria, exclusion criteria, groups, and main results included in each trial are listed in Figure 3[80-83,43].

One of the major reasons we focused on postfracture depression rather than preoperative depression is that the treatment of preoperative depression is similar to that of general depression. Depression in patients with PHFDs can be treated by both physical and psychological approaches because improvements in treating physical function can lead to better relief of depression, and early identification and intervention of risk factors for PHFDs is apparently an optimal choice compared with general depression treatments.

Nurse-led treatment and prevention for PHFDs are not significantly effective: Burns *et al*[80] wanted to determine whether a structured psychiatric intervention (nurse-led) is more effective than treatment as usual (TAU) in reducing depressive symptoms in older people who have depression after hip fracture surgery. Moreover, they explored whether a psychological intervention (cognitive behavior therapy) was more effective than TAU in preventing the development of depression in older people who were free from depressive symptoms immediately after surgery. This was a trial to determine if intervention for depression can treat and prevent its occurrence and progression. In the treatment study, they found a slight reduction in depressive symptoms. In prevention studies, there was no significant difference in the incidence of depression between psychological intervention and conventional treatment. There was also no difference in function or pain outcomes.

In the treatment-of-depression trial, 121 participants scored 7 or higher on the GDS and were allocated to nurse intervention (n = 61) or treatment as usual (n = 60). There were no differences in variables of interest between the two groups at baseline. After six weekly treatments, 28 (52%) in the control group remained depressed, compared with 17 (34%) in the intervention group. This univariate comparison was of only marginal statistical significance (P = 0.10). GDS scores were simultaneously slightly lower (adjusted 6 wk mean 6.3 [intervention group] *vs* 7.1 [control group], mean difference = 0.8; P = 0.11].

In a prevention-of-depression trial, 172 participants scored 6 or lower on the GDS, and 170 were allocated to the cognitive behaviour therapy (CBT) intervention or treatment as usual (n = 85 in each, two participants dropped out before randomization). There were no differences in variables of interest between the two groups at baseline. After the 6 wk follow-up, 4 (6%) of the intervention group had depression, compared with 11 (16%) in the treatment-as-usual group (P = 0.15).

In conclusion, the findings from the abovementioned trials have some implications for clinical practice. The findings of these two trials indicate that interventions do not have a distinct benefit in treating or preventing depression in older people after hip surgery. Neither therapy had a distinct effect on other variables of interest such as pain, functional recovery, or length of stay. Although the nurse-led intervention is ineffective in either preventing or treating depressive symptoms, this study confirmed the rates of depression after surgery for hip fracture found in previous studies and found that poor clinical outcome was related to factors other than depressed mood. Because they may cause lower human and financial expenditures, the therapeutic methods contained in it also have certain reference significance.

Interdisciplinary intervention decreases depressive symptoms, especially the risk of being persistently depressive: Interdisciplinary treatment involves several professionals who independently treat various issues a patient may have, focusing on the

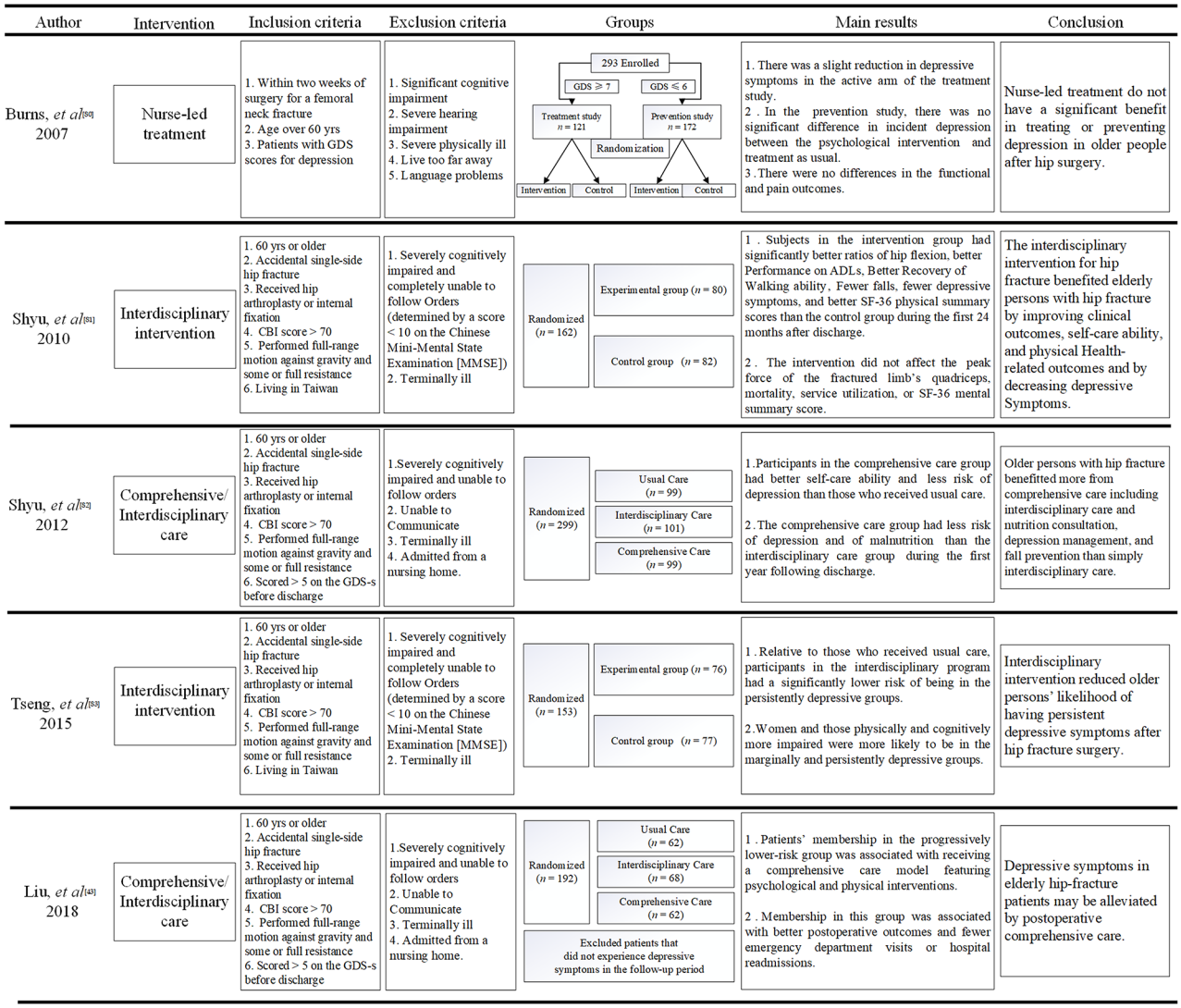


Figure 3 General summary of interventions for postoperative hip fracture depression. The figures in the main results section above refer to Burns *et al*[80], Shyu *et al*[81,82], Tseng *et al*[83] and Liu *et al*[43]. CBI: Caring behavior inventory; GDS: Geriatric depression scale.

issues in which they specialize. Previous studies[84,85] have shown that interdisciplinary interventions can effectively reduce depressive symptoms after hip fracture surgery in the short term. Shyu *et al*[81] reported its long-term effects on variables such as self-reported and performance-based outcomes until the 2nd year after patient discharge. They hypothesized that the clinical benefits of the interdisciplinary intervention would persist into the 2nd year.

The results showed that depressive symptoms decreased significantly over the first 12 mo after discharge, especially within the 6th mo after discharge, which is consistent with the conclusion of previous experiments. Subjects in the intervention group obviously had fewer depressive symptoms than those in the control group (P = 0.05). Over the next 12 mo, although the two groups did not differ significantly in risk for depression at months 12, 18, and 24 after discharge, the severity of depressive symptoms at these time points was greater in the control group than in the intervention group.

In most studies of depressive symptoms among older adults with hip fracture, the focus was on the average change in depressive symptoms over time and how individuals deviate from this average. However, there are actually several broad categories of changes in each person's depression trajectory. Tseng *et al*[83] wanted to determine the distinct trajectories of depressive symptoms over time and the effects of the interdisciplinary intervention on these distinct courses of changes in depressive symptoms. Tseng performed a secondary analysis using data from previous clinical trials to confirm this hypothesis.

After the classification and correlation analyses of patients with different depression trajectories, it was found that participants in the experimental group were less likely to be persistently depressive over the 2-year period of observation, which means that interdisciplinary intervention reduces the risk of being persistently depressive among older patients with hip fracture. However, the interdisciplinary intervention did not apparently reduce the risk of being marginally depressive.

For interdisciplinary care, although there are multidisciplinary combination therapies, the actual benefits are controversial in some studies. Some experiments[86-88] have shown that compared with conventional geriatric care and rehabilitation, interdisciplinary home rehabilitation for older individuals following hip fracture resulted in similar proportions of complications, readmissions, and total days spent in the hospital after discharge. Interdisciplinary approaches to some aspects of patient recovery after hip surgery remain controversial.

Comprehensive care is the optimal solution at present. In recent years, increasing attention has been given to comprehensive nursing after hip fracture in the elderly [89]. At same time, some articles[90-92] have proven that the comprehensive hip fracture program reduced the rate of in-hospital postoperative complications and mortality and improved physical function, role physical, general health, and mental health more than those who received usual care. Improvements in function and a focus on the psyche of the patient with comprehensive treatment can restore the patient's mental state.

Shyu *et al*[82] filled a gap in research on the effectiveness of comprehensive therapy directly on depressive symptoms after hip fracture. They designed a study to compare the consequences of the comprehensive care model with those of the author's previously developed interdisciplinary care model and usual care. They hypothesized that elderly patients who received the comprehensive intervention would have fewer depressive symptoms. After deriving ORs from regression coefficients, they found that the comprehensive care group was 52% less likely to be at risk for depression than the usual care group (OR = 0.48, $P < 0.01$). Similarly, the comprehensive care group was 49% less likely than the interdisciplinary care group (OR = 0.51, $P < 0.05$) to be at risk for depression. In conclusion, researchers' comprehensive care programs with depression management appeared to be more beneficial than interdisciplinary care alone for older persons with hip fracture.

After determining that comprehensive care can reduce the probability risk for depression, Liu and Yang *et al*[43] conducted a secondary analysis of data on a subsample of hip fracture patients at risk for depression. The goal was to examine the associations of membership depressive symptom trajectory groups with receiving the comprehensive care model. Participants belonging to the better postoperative depressive-symptom trajectory group were hypothesized to have received the comprehensive care model. After using a series of analyses to fit trajectory models with two to five trajectory groups, the researchers found that the best fit to the observed data was the model containing two distinct depressive-symptom trajectory groups. To identify the predictors of group membership, they used binary logistic regression modelling and found that patients were likely to be in the progressively lower-risk group if they received comprehensive care than those who received interdisciplinary or usual care (OR = 2.78, 95% CI: 1.00–7.85, $P = 0.05$). Patients in the progressively lower-risk group (approximately 71%) experienced low levels of depressive symptoms that diminished over the 12 mo following surgery.

This analysis is based on a previous experiment, and the conclusion is drawn that comprehensive care featuring both psychological and physical interventions can not only reduce the potential risk for depression but also alleviate depressive symptoms in elderly hip fracture patients.

Both comprehensive intervention and interdisciplinary intervention include a postoperative bedside rehabilitation plan and a postdischarge rehabilitation plan at home. Rehabilitation treatment focuses on the recovery of body function. This is important because depressed patients' functional recovery is mutually affected. Depression worsens the effectiveness of rehabilitation treatment, and poor consequences in turn continue to increase the psychological pressure of patients. This is sure to be a dilemma for most patients after fracture surgery. Therefore, in the treatment of PHFD patients, it is necessary to pay attention to the physiological and psychological recovery of patients. The treatment we give can only be meaningful if both are improved simultaneously. In addition to the rehabilitation program, only the comprehensive care models feature structured management of depressive symptoms, including patients with GDS-s scores > 10 ($n = 4$). Psychiatric consultation was arranged during hospitalization for diagnosis, suggested psychosocial interventions,

and medication management, and a home nurse followed up on patient appointment attendance and adherence to medication regimens. This nurse provided individual consultations, emotional support, and engaged family support for patients with GDS-s scores > 5 (n = 28). However, we cannot confirm the effect of depression management because of the difficulties of teasing out the impact of a single care component within a complex intervention program. Early assessment also plays an important role in both intervention models, and geriatric assessment in the early stage can yield information on developing tailored interventions by identifying the type of depression trajectory. For example, those whose GDS scores at discharge are within the 95% CI (6.5–8.5) may need further interventions for interventions for managing depressive symptoms.

The common shortcoming of both models is that the regions we included in the study cannot generalize the global situation, and the effects of the intervention in this study might not be observed if implemented in Western countries or in Japan, limiting the generalizability of the findings to these nations. A comparison of the three treatment strategies is shown in Table 1.

Management of medication: In terms of medication management, concerns here are that antidepressants can increase the risk of fractures and reduce physical function. Agarwal *et al*[93] compared physical function in current female antidepressant users and nonusers and found that the grip strength of nonusers was 13.3% lower than that of current users (P = 0.04). Wu *et al*[94] demonstrated that depression and antidepressant use are independently linked to an increased risk of fracture. Thus, antidepressant treatment might increase the risk of secondary fractures in patients with PHFDs. Specifically, selective serotonin reuptake inhibitor (SSRI) antidepressants have been associated with reduced bone mineral density, and an increased risk of fragility fracture and tricyclic antidepressants may increase the risk of fracture *via* mechanisms rather than an influence on bone mineral density. However, data on the effects of other antidepressants on bone is insufficient[95]. Older patients, who are particularly vulnerable to osteoporosis, may be preferentially prescribed non-SSRI antidepressants. In conclusion, determining whether antidepressant treatment is required and which antidepressant should be prescribed for specific PHFD patients remains unknown. However, at minimum, PHFD patients should be tested for bone mineral density before medication is prescribed. Subsequent studies should compare the risk-benefit ratio for PHFD patients who take antidepressants to those who do not.

Psychological intervention: To date, we have not found an article demonstrating a specific psychotherapy for PHFDs or a controlled trial to verify its effectiveness. However, given the characteristics of patients after hip fracture (*i.e.* most patients are frail and elderly), some psychological treatment methods for elderly patients with depression can be appropriately adopted. Commonly used and proven psychotherapeutic methods include CBT, behavioral activation therapy, interpersonal psychotherapy, problem-solving therapy (PST), life-review therapy, and nondirective counseling[96]. CBT is a widely used technique in the treatment of depression, and its methods are constantly being innovated to apply to different types of depression patients. However, its core is the therapist through therapeutic interactions and topics of discussion, using a psychoeducational approach, and teaching patients new ways of coping with stressful situations to modify the patient's dysfunctional beliefs (cognitive restructuring) and change their current behaviour as well as future functioning. Huang *et al*[97] demonstrated the effectiveness of CBT through a three-step process in elderly individuals: behavioral scheduling, cognitive assessment and restructuring, and altering dysfunctional beliefs and performing problem-solving strategies. In PST, patients learn how to systematically solve their problems in a number of steps. Kiosses *et al*[98] integrated a problem-solving approach (situation selection, situation modification, attentional deployment, cognitive change, and response modulation) with compensatory strategies, environmental adaptations, and caregiver participation to improve emotional regulation in 74 older adults with depression and found that the participants in problem adaptation therapy had a significantly greater reduction in depression. Life-review therapy is mainly used in older adults and is aimed at balancing positive and negative reminiscences, redefining negative experiences, and elaborating memory. The results of Preschl *et al*[99] indicated that life-review therapy can be recommended for depressive older adults. In the field of psychotherapy for PHFDs, there is still an urgent need for a large amount of experimental data to support the effectiveness of these methods.

Table 1 Comparison of three care models

Content	Usual care	Interdisciplinary care	Comprehensive care
Geriatric consultation	No	Yes	Yes
Rehabilitation program	No	Yes	Yes
Range of motion		Yes	Yes
Muscle strength and endurance		Yes	Yes
Proprioceptive enhancement		Yes	Yes
Balance challenges		No	Yes
Aerobic capacity		No	Yes
On-protocol in-hospital rehab	Yes	Yes	Yes
Nurse rehab visit	Primary Registered nurse	Once per day	Once per day
Physical therapist	Two times	Two times	Two times
On-protocol in-home rehab	No	Yes	Yes
Nurse rehab visit		8 visits in 4 mo	13 visits in 1 yr
PT		3 visits in 4 mo	4 visits in 6 mo
Nutritional consultation/education	No	No	Yes
Depression screening and management	No	No	Yes
Fall prevention	No	Yes	Yes
Discharge planning with post-hospital services	No	Yes	Yes
Modifications (medication recommendations, personal or environmental safety)	No	Yes	Yes

CONCLUSION

Our study found that PHFD, if left untreated, has a significant impact on postoperative recovery. Therefore, preoperative identification of risk factors and postoperative intervention on depressive symptoms themselves are important. Given the current research, patients who have PHFDs may benefit from a comprehensive postoperative care model that features both psychological and physical interventions and an interdisciplinary care model. In addition, interdisciplinary approaches may also be a reasonable choice. More high-quality randomized controlled studies are required to validate current models and explore more effective interventions to further intervene in PHFD.

In this review, we introduced PHFDs and summarized their risk factors and clinical outcomes. In addition, we presented a summary of all previous interventions for depression after hip fracture and summarized the methods and experimental results of interdisciplinary treatment, comprehensive treatment, nurse-led treatment, and usual treatment for doctors' reference. Hip fractures are very common in older people and are associated with high rates of disability and mortality. However, depression following joint fracture surgery is also common and places a greater burden on the patient's recovery. Therefore, it is necessary to have a deep understanding of this kind of concomitant disease and to make correct diagnoses and interventions for a better prognosis.

Serious clinical outcomes may occur if PHFD is not dealt with in a timely manner, which emphasizes more importance in the assessment of risk factors to prevent PHFD. If multiple risk factors exist, then patients should be classified as high-risk, and the depression scale should be evaluated after surgery. This is of great significance for the early identification and intervention of PHFD patients. Therefore, the PHFD scale for preoperative risk factors should be reasonably used in patients. Since there is no unified version of the scale at present, future studies can focus on this aspect.

Patients with high-risk factors should receive appropriate intervention before surgery, rather than after the onset of postoperative depressive symptoms, when it may be too late, the cost of treatment increases, and the effectiveness of treatment

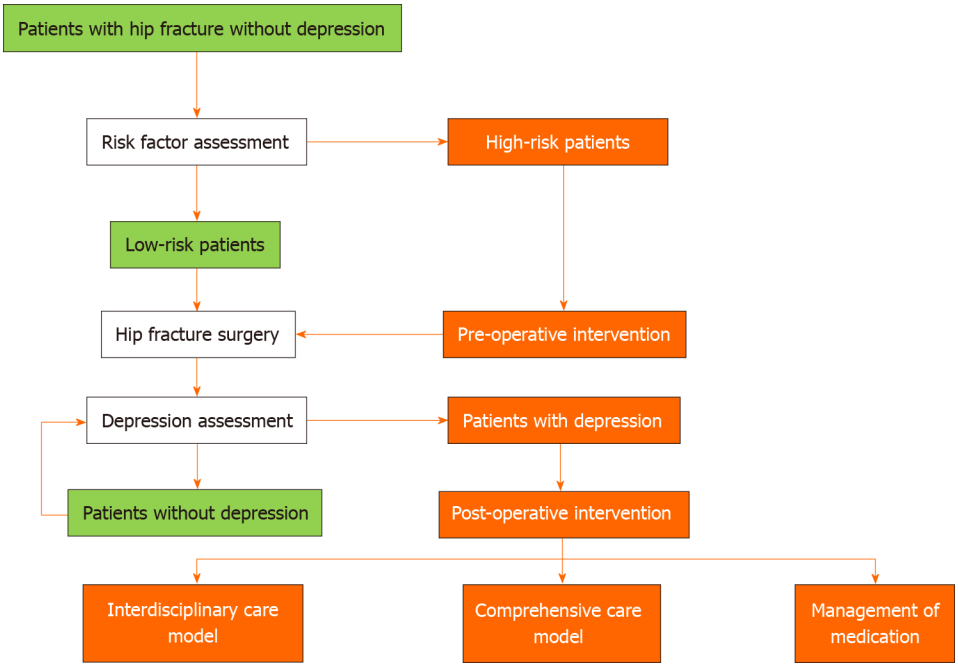


Figure 4 Hypothesis of clinical diagnosis and treatment of postoperative hip fracture depression.

decreases. Subsequent studies may focus on preoperative intervention on the mechanism of PHFD-induced poor outcomes.

What if, after all that, depression still occurs? At present, it seems that interdisciplinary treatment and comprehensive treatment combined with medication therapy are appropriate choices. (See the hypothesis of clinical diagnosis and treatment of PHFD in Figure 4).

However, future research should explore whether global effectiveness means fitting different countries and regions well. To further verify that the treatment regimen is suitable outside of China, it can be tested in countries with similar national conditions, such as Cambodia and India. At the same time, it can also be tried in smaller developed countries such as Singapore to verify the effect of this treatment on countries with different economic development. In this process, treatment patterns will evolve based on local characteristics and eventually produce a version that works for the entire world. A final point should not be overlooked: we need to expand the scope of the research to explore more effective interventions to further treat PHFDs.

ARTICLE HIGHLIGHTS

Research background

The number of hip patients is on the rise, while the number of postoperative depressions is also increasing. The coexistence of the two diseases makes it more difficult for patients to recover their mental and physical functions after surgery, making this a worldwide medical problem.

Research motivation

Clinically, we observed that depression after hip fracture in the elderly is very common and has caused a great burden on patients' families and society. Therefore, we wondered if we could find the best intervention to solve the problem.

Research objectives

The aim was to make doctors more aware of the serious consequences of postoperative hip fracture depression (PHFD). In addition, we hoped to provide a basis for the early detection of PHFDs and recommend treatment methods after occurrence of the disease.

Research methods

We searched four databases for articles related to new depression after hip fracture and classified similar articles.

Research results

In this article, we summarize the risk factors for PHFD and the associated adverse outcomes, which can help to raise awareness of the disease and help with its early diagnosis. At the end of this paper, we summarize the practical and effective interventional methods in clinical practice: Interdisciplinary treatment and comprehensive treatment.

Research conclusions

Preoperative identification of risk factors and postoperative intervention on depressive symptoms themselves are important. In addition, PHFDs may benefit from a comprehensive postoperative care model that features both psychological and physical interventions and an interdisciplinary care model.

Research perspectives

Future research should explore global effectiveness in working with different countries and regions. Moreover, the following need should not be overlooked: we need to expand the scope of the research to explore more effective interventions in order to further treat PHFDs.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 November 19; 11(11): 1147-1166

DOI: 10.5498/wjp.v11.i11.1147

ISSN 2220-3206 (online)

META-ANALYSIS

Effectiveness of cognitive behavioral therapy-based interventions on health outcomes in patients with coronary heart disease: A meta-analysis

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Conflict-of-interest statement: All authors declare no conflict of interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Australia

Specialty type: Psychiatry

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Abstract

BACKGROUND

Recently, the efficacy of cognitive behavioral therapy (CBT)-based intervention on health outcomes in patients with coronary heart disease (CHD) has been recognized in randomized controlled trials (RCTs), but no comprehensive systematic review has been conducted. To address this research gap, our study aimed to evaluate whether comprehensive CBT-based interventions positively affect health outcomes in CHD patients. It was hypothesized that CBT-based interventions are effective in: (1) Reducing depression, anxiety, and stress symptoms; (2) Reducing body mass index, blood pressure, and lipid levels; and (3) Improving quality of life, and exercise endurance.

AIM

To verify the effectiveness of CBT-based interventions on CHD patients through a meta-analysis of previous publications.

METHODS

Relevant RCTs published in English were obtained by searching electronic databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials, Scopus, and Proquest, with the retrieval time from inception to August 2020. The primary outcomes were psychological factors (depression, anxiety, and stress symptoms), physiological factors (body mass index, blood pressure, blood

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: April 9, 2021
Peer-review started: April 9, 2021
First decision: July 14, 2021
Revised: July 27, 2021
Accepted: October 18, 2021
Article in press: October 18, 2021
Published online: November 19, 2021

P-Reviewer: Mizuguchi T, Oei SL
S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

lipids). The secondary outcomes included quality of life and exercise endurance. We used Review Manager 5.3 to conduct the meta-analysis and used the Physiotherapy Evidence Database tool to evaluate the quality of studies.

RESULTS
A total of 22 RCTs comprising 4991 patients with CHD were included in the systematic review and meta-analysis. The main analysis revealed that CBT-based intervention can reduce depression symptoms: -2.00 [95% confidence interval (CI): -2.83 to -1.16, $P < 0.001$]; anxiety symptoms: -2.07 (95%CI: -3.39 to -0.75, $P = 0.002$); stress symptoms: -3.33 (95%CI: -4.23 to -2.44, $P < 0.001$); body mass index: -0.47 (95%CI: -0.81 to -0.13, $P = 0.006$); and improve physical functioning: 3.36 (95%CI: 1.63 to 5.10, $P = 0.000$) and mental functioning: 6.91 (95%CI: 4.10 to 9.73, $P < 0.001$). Moreover, subgroup analysis results showed that CBT-based interventions were more effective for symptoms of depression and anxiety in CHD patients when individual, as opposed to group treatment, and psycho-education, behavioral and cognitive strategies were applied as the core treatment approaches.

CONCLUSION
CBT-based interventions are effective treatment strategies for CHD patients, significantly improving their symptoms of depression, anxiety and stress, body mass index, and health-related quality of life.

Key Words: Coronary heart disease; Cognitive behavioral therapy; Physiological factors; Psychological factors; Quality of life

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Core Tip: This is the first comprehensive meta-analysis examining the effects of critical components of cognitive behavioral therapy (CBT) on improving health outcomes in coronary heart disease (CHD) patients. Our findings suggest that CBT-based interventions were effective in reducing depression, anxiety, stress symptoms, and body mass index levels, and improving physical and mental functioning of the quality of life. In addition, the intervention was more effective when it was delivered as an individual-based treatment, when there was no CHD-specific manual, and when psycho-education, behavioral, and cognitive strategies were applied as the key components of the CBT approach.

Citation: Li YN, Buys N, Ferguson S, Li ZJ, Sun J. Effectiveness of cognitive behavioral therapy-based interventions on health outcomes in patients with coronary heart disease: A meta-analysis. *World J Psychiatr* 2021; 11(11): 1147-1166
URL: https://www.wjgnet.com/2220-3206/full/v11/i11/1147.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i11.1147

INTRODUCTION

Coronary heart disease (CHD), also known as ischemic heart disease, refers to arterial blockage and functional changes of the coronary artery, which then causes myocardial ischemia and hypoxia[1]. CHD patients are prone to have severe physical and mental problems and show the impaired health-related quality of life (QOL)[2], related to high mortality and additional cardiac events[3]. It has been reported that 7.4 million deaths worldwide were due to CHD[4]. Body mass index (BMI), blood pressure, total cholesterol (TC), low-density lipoprotein cholesterol, and glycosylated hemoglobin are important physiological factors observed in patients with CHD[5].

An increasing number of studies have shown that CHD is comorbid with the psychosomatic disease, and mental health plays a significant role in the development and progression of atherosclerosis and heart disease[6]. Doering *et al*[7] undertook a longitudinal cohort study with 2325 patients with stable CHD and found that depression and anxiety symptoms increased the risk of death in participants. Pająk *et*

al[8] found a high prevalence of depression and anxiety in CHD patients, and that these psychological factors were negatively associated with favorable lifestyle changes, which were not conducive to CHD rehabilitation. A review by Cohen *et al*[9] indicated that chronic anxiety and exposure to daily stressors harmed cardiovascular health. The aggressive treatment of depression and anxiety is imperative because of the association of these factors with decreased medication compliance[10], lifestyle change adherence, and an increased risk of mortality[11].

Cognitive behavioral therapy (CBT) has been increasingly used to modify cardiovascular risk factors in psychosocial intervention programs[12,13] and to reduce psychosocial risk factors, including depression, anxiety, and loneliness, in patients with heart disease[14]. In general, CBT is a psychological therapy based on the hypothesis that cognitive processes affect emotion and behavior. Therefore, changing non-adaptive thought patterns and beliefs will lead to positive behavioral changes [15]. However, the effects of CBT on improving health outcomes in CHD patients are inconsistent. For instance, a cardiac rehabilitation program[16] showed that CBT was associated with significant improvement in depressive symptoms and high-density lipoprotein cholesterol (HDL-C). Similarly, Magán *et al*[17] found that psychological outcomes in CHD patients were improved when a CBT approach was implemented. However, Turner *et al*[18] found no differences between CBT and control groups on change in depression or anxiety symptoms in cardiac patients. Additionally, in most meta-analyses conducted to date, there has been no detailed analysis of the critical components of CBT affecting patients with CHD.

To address the research gap, this study aimed to evaluate whether CBT-based interventions are effective in reducing depression, anxiety and stress symptoms, BMI, blood pressure, and lipids level, improving QOL, and exercise endurance in CHD patients.

MATERIALS AND METHODS

We conducted this meta-analysis following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. In addition, we registered the research protocol at the PROSPERO International Prospective Register of Systematic Reviews (Registration ID: CRD42020213587 PROSPERO 2020 website: https://www.crd.york.ac.uk/prospero/#recordDetails). We did not need to get Ethical Approval or Patient Consent for this study, because it was a systematic review and meta-analysis based on the previous publications.

Search strategy

The databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials, Scopus, Proquest, were searched separately by two researchers. The keywords of "coronary heart disease" or "unstable angina" or "percutaneous coronary intervention" or "coronary artery bypass graft" or "acute coronary syndrome" or "myocardial infarction" and "cognitive behavioral therapy" were used to do the literature retrieval. We used the subject words + free words with Boolean operators AND/OR to search for target articles in abstracts, keywords, or titles, and the language was limited to English. In the search process, we modified the search terms appropriate for different search rules of various databases. The specific retrieval strategy was in the supplementary file. The reference lists of the publications were searched to find additional relevant articles. The retrieved time was restricted from its inception to August 2020. We used the Endnote X8 Software (Clarivate Analytics, PA, United States) to manage the collected literature. The literature search was conducted separately by two researchers. When there was a disagreement between the two researchers, a third researcher was invited to join in the discussion to resolve the disagreement.

Study selection

Inclusion criteria were developed using the PICOS approach: (1) P: The target population was adult patients aged 18 and above and with diagnosed CHD, regardless of disease stage and severity. Eligible patients included those with unstable angina, those who had undergone percutaneous coronary intervention or coronary artery bypass graft, and patients with the acute coronary syndrome or those who had suffered a myocardial infarction; (2) I: The principles of CBT had to be applied to the intervention, including both cognitive and behavioral techniques, such as recognition and diagnosis of automatic thinking, behavior experiment, behavior activation,

cognitive restructuring, and emotional modulation. A separate CBT or CBT combined with other methods was acceptable. The delivery of intervention could be face-to-face or remote, and the intervention form could be individual or group-based; (3) C: The control groups could be the non-CBT interventions, or usual care or waiting list. The usual care group was chosen if there were multiple comparison groups; (4) O: The main outcomes were psychological factors, including depression, anxiety, and stress symptoms; physiological factors, including BMI, blood pressure, lipids level: Low-density lipoprotein cholesterol, HDL-C, triglycerides, TC. The secondary outcomes were QOL and exercise endurance. 6-Minute Walk Distance Test was used to assess the exercise endurance. The article reporting one or more of the above outcomes was included; (5) S: We included the randomized controlled trial (RCT), with no limitation on follow-up time; (6) Only English articles; and (7) Accessibility of full-text publication.

Studies were excluded based on the following criteria: (1) Comprising solely cognitive or behavioral therapies; (2) No report on quantitative analyses; (3) All reviews and protocols; (4) Literature with incomplete data and inconsistent statistical methods; (5) Duplicate publications, we only included the most relevant study; (6) Low-quality studies, whose score of Physiotherapy Evidence Database tool (PEDro) ≤ 3; (7) Not English articles; or (8) Not a peer-reviewed journal article.

Data extraction

We extracted data by using a data-collection form, which included the following information: The name of the first author, publication year, research location, research subjects (sample size, age, sex, the type of diseases), research design, intervention method, control method, and outcome factors. Where data was incomplete, the corresponding author was contacted to obtain the data.

Quality assessment

The full texts of included articles were read by two reviewers independently and PEDro tool[19] was used to evaluate their methodological quality. There were ten items in PEDro tool: Subjects were randomly grouped; randomization was concealed; the baseline information between groups was similar; subjects, researchers, and assessors were blinded; low drop-out rate; "intention to treat" principle was used; the variability measures were used; between-group comparison methods were used. The quality of studies is categorized into three levels based on the ten items of PEDro tool: Research with eight points and above is high quality, with four to seven is medium quality, with three and less than three is low quality. The disagreements on the quality rating of the included study were resolved through consultation with a third researcher.

Statistical analysis

Review Manager 5.3 was used for the meta-analysis. We did a separate meta-analysis for each outcome variable. We used the pooled mean difference (MD) with a 95% confidence interval (CI) for continuous outcome variables and used the standardized MD (SMD) with 95%CI to measure their effect size. The effect size was small if SMD was between 0.2 and 0.5. When SMD ranged from 0.5 to 0.7, the effect size was medium. And the effect size was large when SMD was more than 0.7. The threshold was set as 0.05 and two-sided.

We used the Chi-square test and I^2 for heterogeneity testing. If $I^2 < 50\%$ or $P > 0.05$, homogeneity was considered to be good among the included studies, and the fixed-effect model was adopted. If $I^2 > 50\%$, studies were assessed as having a high level of heterogeneity, and the random-effect model was adopted.

Publication bias was evaluated using the Egger test using Stata Statistical Software 15. There was a statistical publication bias if the P value was less than 0.05. In addition, we used the funnel plot to analyze whether there was publication bias if the number of meta-analysis studies exceeded 10.

Subgroup analyses were conducted for depression and anxiety symptoms in CHD patients to find the underlying factors that led to heterogeneity and to figure out the effective components of CBT. We evaluated the pooled MD for each subgroup and used the Q statistics to examine the differences in MD. The subgroups were as follow: The treatment form (individual or group); treatment course (< 12 wk or ≥ 12 wk); duration of a session (< 50 min or ≥ 50 min); the number of sessions (< 10 or ≥ 10); mode of delivery (face-to-face or remote); use of a CHD-specific manual (yes or no); drop-out rate (< 20% or ≥ 20%); the intervention group used specific techniques of CBT (yes or no). We categorized the specific techniques for CBT based on the Compre-

hensive Psycho-therapeutic Intervention Rating Scale and previous studies[20-23], which included psycho-education, behavioral strategies, cognitive strategies, affective strategies, interpersonal strategies, exposure, body-directed strategies, behavior experiment, mindfulness and attention, homework assignment. If the intervention technique was mentioned as an important technique, it was identified as "yes", otherwise it was identified as "no".

RESULTS

Literature search

As shown in Figure 1, we found 1293 articles, including 1289 articles from the database search and four articles from references in the publications. After removing duplicates, there were 916 articles left for the title and abstract screening. Of these, we discarded 793 publications that did not meet the inclusion criteria. Then, 123 articles were left for the full-text screening. Two researchers independently did the full-text evaluation in strict accordance with the inclusion rules. Through full-text screening, 101 articles were excluded, and the specific process of identifying relevant articles for inclusion in the systematic review and meta-analysis was described in Figure 1, resulting in 22 studies being included in this meta-analysis.

Study characteristics

Full details of the included studies were displayed in Table 1. Four thousand nine hundred and ninety-one participants were included in the 22 RCTs: 2443 in the intervention group and 2548 in the control group. The mean age of the intervention group was 59.57 and 59.85 in the control group. Five[24-28] of these studies were carried out in developing countries and 17[14,16,18,29-42] in developed countries. The intervention group used CBT or CBT-based intervention and the control group adopted usual care methods activity methods. Five studies[34,38-41] used remote interventions, such as through the internet or telephone, and 17[14,16,18,24-33,35-37,42] used traditional face-to-face interventions. Twelve[16,24-26,29,32-34,38-40,42] studies used an individual CBT intervention, eight studies[18,27,30,31,35-37,41] used a group-based CBT intervention, and one[14] used both. Only six studies[18,24,29,33,37,41] reported using an instruction manual. Five types of outcomes were included in the analysis: physiological factors, psychological factors, QOL, exercise endurance, and cardiac rehabilitation factors. Six studies[16,31,34,37,41,42] reported physiological factors, 20 studies[14,16,18,25-36,38-42] reported psychological factors, 10[24,25,30-34,39,40,42] reported QOL, two[37,41] reported exercise endurance, and four[16,24,31,37] reported cardiac rehabilitation factors. However, due to the differences in cardiac rehabilitation factors, a meta-analysis could not be performed. The mean drop-out rate for the intervention group was 12.49% and 11.09% for the control group. Table 1 showed the characteristics of intervention methods and control methods in detail.

Post- to pre-treatment effects of CBT-based intervention

Effects on psychological factors: Eighteen studies[14,16,18,25,27,29-36,38-42] analyzed the effect of CBT-based intervention on depression symptoms in 3579 participants. The number of intervention and control group participants was 1798 and 1781, respectively. Results showed a significant improvement in depression symptoms, with a reduction of depression symptoms of -2.00 (95%CI: -2.83 to -1.16, $P < 0.001$), and a small effect size of SMD -0.42 (95%CI: -0.60 to -0.24, $P < 0.001$). There was statistical heterogeneity across the 18 studies ($I^2 = 83\%$, $P < 0.001$) (Table 2). The forest plot of the effect was shown in Figure 2A.

Subgroup analyses (Table 3) found that CBT-based intervention was more effective on improving depression symptoms when it was individual treatment form, when there was no CHD-specific manual, and when the drop-out rate was < 20%. CBT-based interventions statistically reduced depression symptoms when they emphasized psycho-education, behavioral and cognitive strategies as the core approaches. In addition, CBT-based intervention was more effective when it did not highlight affective or interpersonal strategies.

The effect on anxiety symptoms was analyzed in 14 studies[16,18,25,27-30,32,33,36,38,40-42] with 1293 patients. There were 639 patients in the intervention group and 654 in the control group. The meta-analysis showed that CBT-based interventions significantly alleviated anxiety symptoms, with a reduction of symptom mean of -2.07 (95%CI: -3.39 to -0.75, $P = 0.002$), and a small effect size of -0.42 (95%CI: -0.72 to -0.11, $P = 0.008$). The heterogeneity was significant among the studies ($I^2 = 91\%$, $P < 0.001$)

Table 1 Characteristics of randomized controlled trials included in this meta-analysis

Ref.	Country	Sample size (I/C)	Gender: female, *n* (%)	Age (mean ± SD)	CHD diagnosis	Intervention	Format	Manual	Control group	Outcome	Measurement	Drop-out rate (%)	Quality of article
Barth *et al*[29], 2005	Germany	59 (27/32)	I: 5 (18.50) C: 9 (28.10)	I: 60.81 ± 11.06 C: 55.62 ± 10.05	MI; CABG; PTCA; Unstable Angina Pectoris	CBT based intervention	Individual	Yes	UC	(2)	BDI; HADS	I: 0.00 C: 12.50	7 (moderate)
Beresnevaitė *et al*[24], 2016	Lithuania	150 (79/71)	I: 13 (30.20) C: 14 (30.40)	I: 56.70 ± 10.20 C: 59.10 ± 11.10	CABG; valve replacement; valve repair surgery	CBT	Individual	Yes	UC	(3), (5)	SF36	I: 45.57 C: 35.21	4 (moderate)
Berkman *et al* [14], 2003	United States	2481 (1238/1243)	I: 532 (43.00) C: 552 (44.00)	I: 61.00 ± 12.60 C: 61.00 ± 12.50	MI	CBT	Individual + group	No	UC	(2)	BDI	I: 7.51 C: NR	7 (moderate)
Blumenthal *et al*[30], 2016	United States	151 (76/75)	I: 31 (41.00) C: 24 (32.00)	I: 61.80 ± 10.80 C: 60.40 ± 10.60	ACS; stable angina; coronary revascularization	CR + SMT	Group	No	CR	(2), (3)	BDI-II; STAI; PSS; GHQ	I: 3.95 C: 4.00	7 (moderate)
Claesson *et al* [31], 2006	Sweden	198 (101/97)	I: 101 (100.00) C: 97 (100.00)	I: 59.40 ± 9.30 C: 62.20 ± 7.70	AMI; CABG; coronary angioplasty; angina pectoris	CBT based intervention	Group	No	UC	(1), (2), (3), (5)	ELSS; CPRS-S-A	I: 23.76 C: 15.46	6 (moderate)
Dao *et al*[32], 2011	United States	100 (50/50)	I: 11 (22.90) C: 10 (20.40)	I: 62.80 ± 11.80 C: 64.20 ± 11.90	A CAD diagnosis and were scheduled to undergo a first-time CABG	CBT	Individual	No	UC	(2), (3)	BDI-II; STAI SF12	I: 4.00 C: 4.00	6 (moderate)
Freedland *et al* [33], 2009	United States	123 (41/42/40)[1]	I: 23 (56.00) C1: 21 (50.00) C2: 17 (43.00)	I: 62.00 ± 11.00 C1: 59.00 ± 10.00 C2: 61.00 ± 9.00	CABG	CBT + UC	Individual	Yes	SSM+ UC; UC	(2), (3)	BDI; BAI PSS; SF36	I: 2.44 C1: 11.90 C2: 7.50	7 (moderate)
Javaheri *et al* [34], 2020	United States	34 (18/16)	I: 7 (38.89) C: 2 (12.50)	I: 70.30 ± 10.00 C: 72.90 ± 9.20	MI; coronary artery revascularization; angiographically documented stenosis of a major coronary artery	General sleep education + web-based CBT	Individual	No	Wait-list	(1), (2), (3)	PHQ-8; Duke Health Profile	I: 16.67 C: 11.11	5 (moderate)
Koertge *et al* [38], 2008	Sweden	247 (119/128)	I: 119 (100.00) C: 128 (100.00)	I: 61.36 ± 9.10 C: 62.73 ±	AMI; PCI; CABG	CBT based intervention	Group	No	UC	(2)	BDI	I: 17.65 C: 20.31	7 (moderate)

				8.72								
Lv *et al*[25], 2016	China	75 (38/37)	I: 12 (31.58) C: 10 (27.03)	I: 52.40 ± 6.30 C: 52.00 ± 6.20	PCI	CBT + UC	Individual	No	UC	(2), (3)	HAM-D HAM-A CROQ-PTCA-POST	I: 0.00 C: 0.00	6 (moderate)
Merswolken *et al*[36], 2011	Germany	62 (30/32)	I: 6 (24.00) C: l8 (30.00)	I: 62.50 ± 8.30 C: 59.80 ± 7.50	MI; angiographically documented CHD	CBT based intervention	Group	No	Blank control	(2)	HADS	I: 16.67 C:15.63	5(moderate)
Murphy *et al* [37], 2013	Australia	275 (139/136)	I: 15 (10.79) C: 22 (16.18)	I: 58.02 ± 8.87 C: 59.92 ± 9.27	MI; CABG; PCI	CBT	Group	Yes	UC	(1), (4), (5)	6MWT	I: 14.39 C: 16.91	7 (moderate)
Nehra *et al*[26], 2012	India	50 (25/25)	NR	NR	MI; AP	CBT	Individual	No	UC	(2)	PSS	I: 0.00 C: 0.00	5 (moderate)
Nejati *et al*[27], 2020	Iran	51 (17/17/17)[2]	I: 7 (41.18) C1: 4 (23.53) C2: 5 (29.41)	I: 59.00 ± 10.48 C1: 57.00 ± 9.17 C2: 58.00 ± 9.77	CABG; coronary angiography	CBTG	Group	No	CTG; UC	(2)	BDI-II; DASS-21	I: 0.00 C: 0.00	6 (moderate)
Norlund *et al* [38], 2018	Sweden	239 (117/122)	I: 44 (37.60) C: 36 (29.50)	I: 58.40 ± 9.00 C: 60.80 ± 7.80	MI	iCBT	Individual	No	UC	(2)	HADS	I: 17.95 C: 5.74	7 (moderate)
O'Neil *et al* [39], 2014	Australia	121 (61/60)	I: 16 (26.20) C:14 (23.30)	I: 61.00 ± 10.20 C: 58.90 ± 10.70	ACS; unstable angina	CBT based intervention(telephone)	Individual	No	UC	(2), (3)	PHQ-9;SF-12	I: 13.11 C: 11.67	9 (high)
Rafanelli *et al* [16], 2020	Italy	100 (50/50)	I: 19 (38.00) C: 12 (24.00)	I: 57.64 ± 9.99 C: 60.02 ± 10.94	MI; unstable angina	CBT + WBT	Individual	No	CM	(1), (2), (5)	SQ	I: 16.00 C: 20.00	7 (moderate)
Schneider *et al* [40], 2020	Canada	53 (25/28)	I: 12 (48.00) C: 19 (67.90)	I: 56.72 ± 11.90 C: 59.29 ± 6.93	MI; unstable angina	iCBT	Individual	No	Wait-list	(2), (3)	PHQ-9;GAD-7; DASS-21;SF-12	I: 12.00 C: 7.14	7 (moderate)
Turner *et al* [18], 2013	Australia	57 (25/32)	I: 6 (24.00) C: 5 (28.13)	I: 61.00 ± 11.00 C: 62.00 ± 9.00	ACS; PCI; CABG	CBT	Group	Yes	BI	(2)	BDI-II;HADS-A	I: 16.00 C: 3.13	7 (moderate)
Turner *et al* [41], 2014	Australia	42 (21/21)	I: 3 (14.29) C: 6 (28.57)	I: 55.60 ± 8.80 C:	AMI; CABG; PCI	iCBT	Group	Yes	UC	(1), (2), (4)	BDI-II; HADS-A 6MWT	I: 28.57 C: 23.81	5 (moderate)

				57.00 ± 11.20									
Zeighami *et al* [28], 2018	Iran	90 (30/30/30)[3]	I: 10 (33.33) C1: 9 (29.90) C2: 12 (40.10)	47.62 ± 8.93	MI	CBT	Nr	No	EMDR	(2)	BAI	NR	4 (moderate)
Zetta *et al*[42], 2011	United Kingdom	233 (116/117)	I: 31 (28.00) C: 38 (35.00)	I: 64.80 ± 10.04 C: 65.94 ± 9.96	Angina	CBT based intervention	Individual	No	UC	(1), (2), (3)	HADS; SF-36	I: 6.03 C: 6.84	7 (moderate)

[1]I = Cognitive behavioral therapy (CBT) + usual care (UC); C1 = Supportive stress management (SSM) + UC; C2 = UC.
[2]I = Cognitive-behavioral group intervention; C1 = Cognitive therapy in groups; C2 = UC.
[3]I = CBT; C1 = Eye movement desensitization reprocessing; C2 = control group.
Outcome: (1) Physiological factors (BMI, blood pressure, blood lipid profile: LDL-C, HDL-C, TG, TC); (2) Psychological factors (depression, anxiety, and stress symptoms); (3) QOL; (4) Exercise endurance; and (5) Cardiac rehabilitation. UC: Usual care; SSM: Supportive stress management; EMDR: Eye movement desensitization reprocessing; CBTG: Cognitive-behavioral group intervention; MI: Myocardial infarction; AMI: Acute myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; ACS: Acute coronary syndrome; PTCA: Percutaneous transluminal coronary angioplasty; AP: Angina pectoris; iCBT: Internet-cognitive behavioral therapy; CR: Cardiac rehabilitation; SMT: Stress management training; WBT: Well-being therapy; CM: Clinical management; BI: No further intervention; NR: No report; BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; SF-36: 36-Item Short Form Health Survey; BDI-II: Beck Depression Inventory II; STAI: State-Trait Anxiety Inventory; PSS: Perceived Stress Scale; GHQ: General Health Questionnaire; ELSS: The Everyday Life Stress Scale; CPRS-S-A: Comprehensive Psychopathological Rating Scale Self-Affective; SF-12: Short Form-12 Health Survey; BAI: Beck Anxiety Inventory; PHQ-8: Patient Health Questionnaire-8; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Scale; CROQ-PTCA-POST: Coronary Revascularization Outcome Questionnaire; 6MWT: 6-Minite Walk Distance Test; DASS-21: Depression Anxiety, Stress Scales; PHQ-9: Patient Health Questionnaire-9; SQ: Symptom Questionnaire; GAD-7: General Anxiety Disorder 7-Item.

(Table 2). Figure 2B showed the forest plot of the effect.

Similarly, subgroup analyses (Table 4) found that CBT-based intervention was more effective for anxiety symptoms when it was individual treatment form, longer duration of a session (≥ 50 min), less than 10 sessions (< 10), face-to-face treatment delivery, and no use of CHD-specific manual. As for CBT technique components, CBT-based intervention was more effective when it applied the following techniques as the core strategies: psycho-education, behavioral and cognitive strategies. In addition, CBT-based interventions that did not use interpersonal strategy as the core approach showed a better effect on reducing anxiety symptoms.

Five studies[26,27,30,33,40] with a total participant number of 369 analyzed the effect of CBT on stress symptoms. There were 184 patients in the intervention group and 185 in the control group. CBT-based interventions improved stress symptoms significantly with a pooled MD of -3.33 (95%CI: -4.23 to -2.44, $P < 0.001$) and a medium effect size of -0.62 (-0.83 to -0.40, $P < 0.001$). There was no significant heterogeneity between these studies ($I^2 = 22\%$, $P = 0.280$) (Table 2). Figure 2C presented the forest plot of the effect.

Effects on physiological factors: The effect of CBT-based intervention on BMI was analyzed in two studies[31,42] with 377 patients. There were 186 participants in the intervention group and 191 in the control group. Results showed that CBT-based

Table 2 Total effect of cognitive behavioral therapy -based interventions on depression, anxiety, stress symptoms, body mass index, blood pressure, total cholesterol, high-density lipoprotein cholesterol, quality of life, and 6-min walk test distance

Index	Outcomes: Post-to pre-treatment effect							
	Studies, *n*	Participant	I^2 % (*P* value)	*Q*-test	MD (95%CI)	*P* value	SMD (95%CI)	*P* value
Depression	18	3579	83 (< 0.001)	102.69	-2.00 (-2.83, -1.16)[c]	< 0.001	-0.42 (-0.60, -0.24)[c]	< 0.001
Anxiety	14	1293	91 (< 0.001)	142.05	-2.07 (-3.39, -0.75)[b]	0.002	-0.42 (-0.72, -0.11)[b]	0.008
Stress	5	369	22 (0.280)	5.11	-3.33 (-4.23, -2.44)[c]	< 0.001	-0.62 (-0.83, -0.40)[c]	< 0.001
BMI	2	377	0 (0.550)	0.36	-0.47 (-0.81, -0.13)[b]	0.006	-0.23 (-0.43, -0.02)[a]	0.030
Systolic pressure	4	437	1 (0.390)	3.04	-1.82 (-5.12, 1.49)	0.280	-0.10 (-0.29, 0.09)	0.290
Diastolic pressure	4	437	0 (0.870)	0.72	-0.95 (-2.75, 0.86)	0.300	-0.09 (-0.28, 0.09)	0.330
TC	2	131	0 (0.390)	0.75	0.15 (-0.81, 1.12)	0.760	0.15 (-0.19, 0.50)	0.380
HDL-C	2	131	0 (0.890)	0.02	0.07 (-0.09, 0.23)	0.390	0.05 (-0.29, 0.40)	0.760
Physical function	7	666	49 (0.070)	11.77	3.36 (1.63, 5.10)[c]	0.000	0.27 (0.12, 0.43)[b]	0.001
Mental function	5	419	52 (0.080)	8.28	6.91 (4.10, 9.73)[c]	< 0.001	0.71 (0.41, 1.00)[c]	< 0.001
6-minute walk test distance	2	279	0 (0.550)	0.35	9.64 (-11.80, 31.08)	0.380	0.11 (-0.13, 0.34)	0.380

[a]$P < 0.05$
[b]$P < 0.01$
[c]$P < 0.001$.
MD: Mean difference; SMD: Standard mean difference; BMI: Body mass index; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; CI: Confidence interval.

intervention was more effective for reducing BMI levels than for the control conditions, with a mean reduction of BMI of -0.47 (95%CI: -0.81 to -0.13, $P = 0.006$), and a small effect size -0.23 (95%CI: -0.43 to -0.02, $P = 0.030$). There was no significant heterogeneity between these studies ($I^2 = 0\%$, $P = 0.550$) (Table 2). Figure 3A presented the forest plot of the effect.

The effect of CBT-based intervention on blood pressure was analyzed in four studies[31,34,41,42]. There were 216 patients in the intervention group and 221 in the control group. The meta-analysis did not show a significant reduction either in systolic pressure (-1.82, 95%CI: -5.12 to 1.49, $P = 0.280$) or diastolic pressure (-0.95, 95%CI: -2.75 to 0.86, $P = 0.300$). Additionally, there was not significant heterogeneity for systolic blood pressure ($I^2 = 1\%$, $P = 0.390$) or diastolic blood pressure ($I^2 = 0\%$, $P = 0.870$) (Table 2). Figure 3B and C presented the forest plot of the effect.

Two studies[16,41] with 131 with 131 patients measured the effect on TC and HDL-C. There were 65 and 66 participants in the intervention and control group. We did not find a significant reduction in TC (0.15, 95%CI: -0.81 to 1.12, $P = 0.760$). Similarly, we did not find a significant improvement in HDL-C (0.07, 95%CI: -0.09 to 0.23, $P = 0.390$). There was not significant heterogeneity for TC ($I^2 = 0\%$, $P = 0.390$) or HDL-C ($I^2 = 0\%$, $P = 0.890$) (Table 2). Figure 3D and E showed the forest plot of the effect.

Effects on QOL and exercise endurance: The effect on physical function of the QOL was analyzed in seven studies[24,25,33,34,39,40,42] with 666 subjects. There were 332 and 334 patients in the intervention and control groups. Results showed that CBT-based interventions significantly improved physical function across seven studies with improved MD of 3.36 (95%CI: 1.63 to 5.10, $P = 0.000$) and a small effect size of 0.27 (0.12 to 0.43, $P = 0.001$). The heterogeneity between these studies was not significant ($I^2 = 49\%$, $P = 0.070$) (Table 2). Figure 4A showed the forest plot of the effect.

The effect on the mental function of the QOL was analyzed in five studies[24,25,33,39,40] with 419 patients. There were 208 patients in the intervention group and 211 in the control group. The pooled MD of improvement of mental function for CBT was 6.91 (95%CI: 4.10 to 9.73, $P < 0.001$) and a large effect size of 0.71 (0.41 to 1.00, $P <$

Table 3 Subgroup analysis on the effect of cognitive behavioral therapy-based interventions on depression symptoms

Subgroups	Depressive symptom: Post- to pre-treatment effect						
	Studies (*n*)	Participants (*n*)	I^2 % (*P* value)	*Q*-test	MD (95%CI)	SMD (95%CI)	*P* value (between)
Treatment form							0.030
Group	8	2581	72 (0.001)	24.86	-0.96 (-2.16, 0.24)	-0.17 (-0.32, -0.02)[a]	
Individual	10	1061	88 (< 0.001)	75.51	-2.97 (-4.33, -1.62)[c]	-0.66 (-0.97, -0.35)[c]	
Treatment course							0.200
≥ 12 wk	11	3194	81 (< 0.001)	51.97	-1.28 (-2.07, -0.50)[b]	-0.34 (-0.54, -0.14)[c]	
< 12 wk	6	288	68 (0.008)	15.69	-2.83 (-5.08, -0.57)[a]	-0.54 (-1.05, -0.02)[a]	
Duration of a session							0.070
≥ 50 min	11	2788	84 (< 0.001)	62.43	-2.25 (-3.68, -0.81)[b]	-0.34 (-0.55, -0.13)[b]	
< 50 min	3	439	13 (0.320)	2.30	-0.86 (-1.36, -0.35)[c]	-0.46 (-1.11, 0.19)	
Number of sessions							0.330
≥ 10	9	2876	82 (< 0.001)	43.75	-1.62 (-2.76, -0.49)[b]	-0.28 (-0.45, -0.12)[c]	
< 10	8	485	80 (< 0.001)	35.88	-2.90 (-5.22, -0.59)[a]	-0.50 (-0.92, -0.09)[b]	
Treatment delivery way							0.410
Remote	5	473	81 (0.000)	20.63	-2.73 (-4.78, -0.67)[b]	-0.58 (-0.97, -0.19)[b]	
Face to face	13	3106	85 (< 0.001)	77.45	-1.77 (-2.78, -0.77)[c]	-0.37 (-0.59, -0.16)[c]	
Manual available							0.610
Yes	4	212	84 (0.000)	19.24	-3.27 (-9.09, 2.55)	-0.39 (-1.07, 0.30)	
No	14	3367	83 (< 0.001)	76.32	-1.76 (-2.56, -0.96)[c]	-0.42 (-0.62, -0.23)[c]	
Drop-out							0.610
≥ 20%	2	197	34 (0.220)	1.51	-1.31 (-4.21, 1.59)	-0.23 (-0.51, 0.05)	
< 20%	16	3382	85 (< 0.001)	100.58	-2.10 (-3.04, -1.17)[c]	-0.44 (-0.64, -0.24)[c]	
Psycho-education strategies							0.440
Important	15	3367	82 (< 0.001)	76.48	-1.78 (-2.59, -0.97)[c]	-0.40 (-0.59, -0.21)[c]	
Not important	3	212	92 (< 0.001)	24.52	-4.60 (-11.79, 2.58)	-0.54 (-1.37, 0.28)	
Behavioral strategies							0.005
Important	13	3315	87 (< 0.001)	95.77	-2.48 (-3.47, -1.48)[c]	-0.52 (-0.73, -0.31)[c]	
Not important	5	264	11 (0.340)	4.50	-0.30 (-1.45, 0.85)	-0.05 (-0.30, 0.20)	
Cognitive strategies							0.670
Important	16	3448	85 (< 0.001)	99.64	-2.11 (-2.99, -1.23)[c]	-0.45 (-0.64, -0.26)[c]	
Not important	2	131	53 (0.150)	2.11	-1.18 (-5.38, 3.03)	-0.14 (-0.65, 0.37)	
Affective strategies							0.005
Important	2	413	0 (0.680)	0.18	-0.49 (-1.32, 0.34)	-0.09 (-0.29, 0.10)	
Not important	16	3166	85 (< 0.001)	100.55	-2.32 (-3.30, -1.33)[c]	-0.47 (-0.68, -0.27)[c]	
Interpersonal strategies							0.230
Important	4	2422	80 (0.002)	15.31	-1.29 (-2.67, 0.09)	-0.21 (-0.37, -0.05)[b]	
Not important	14	1157	84 (< 0.001)	80.72	-2.40 (-3.55, -1.25)[c]	-0.52 (-0.79, -0.24)[c]	

Body directed strategies							0.070
Important	9	2876	70 (0.001)	26.46	-1.20 (-1.91, -0.49)[c]	-0.33 (-0.53, -0.12)[b]	
Not important	9	703	88 (< 0.001)	66.33	-3.47 (-5.84, -1.10)[b]	-0.54 (-0.92, -0.17)[b]	
Homework assignment strategies							0.890
Important	6	2314	83 (< 0.001)	29.48	-2.07 (-3.75, -0.38)[b]	-0.32 (-0.60, -0.05)[a]	
Not important	12	1265	80 (< 0.001)	55.64	-1.93 (-2.96, -0.90)[c]	-0.47 (-0.74, -0.20)[c]	

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
MD: Mean difference; SMD: Standard mean difference; CI: Confidence interval.

0.001). There was significant heterogeneity between these studies (I^2 = 52%, P = 0.080) (Table 2). The forest plot of the effect was presented in Figure 4B.

Two studies[37,41] with 279 patients measured the change in exercise endurance. The number of intervention and control group participants was 146 and 133, respectively. We did not find a significant distance change between CBT-based interventions and control conditions (9.64, 95%CI: -11.80 to 31.08, P = 0.380). There was no significant heterogeneity between these studies (I^2 = 0%, P = 0.550). The forest plot of the effect was presented in Figure 4C.

Risk of bias and quality assessment

The PEDro tool was used to evaluate the methodology quality of included studies, with one being high quality, accounting for 4.55%, and the remaining 21 being medium quality, accounting for 95.45%. Specifically, one study[39] scored 9, 11 studies [14,16,18,29,30,33,35,37,38,40,42] scored 7, four studies[25,27,31,32] scored 6, four studies[26,34,36,41] scored 5, and two studies[24,28] scored 4.

Publication bias

There was no T or P value of Egger analysis for BMI, TC, and HDL-C, because only two studies reported the results of CBT-based interventions on these variables. In Table 5, there was a minimal publication bias in the following outcome variables: depression symptoms (P = 0.467), anxiety symptoms (P = 0.196), systolic pressure (P = 0.516), diastolic pressure (P = 0.836), physical function (P = 0.829), and mental function (P = 0.135). However, the publication bias for stress symptoms (P = 0.021) was significant. We used the one-study-removed methods to evaluate the sensitivity, and we found that the overall results for all outcome variables were not changed when removing one study at a time. The funnel plots were in the Figure 5.

DISCUSSION

The results of our meta-analysis showed that CBT-based interventions were superior to the usual care controls. They reduced depression, anxiety, and stress symptoms, BMI levels, and improved physical and mental functioning in relation to the QOL. In addition, our subgroup analyzed several key identified components of CBT interventions that influenced their effect.

Post- to pre-treatment effects of CBT-based intervention

Effects on Psychological factors: Similar to previous studies[30,40], our study found that CBT-based intervention effectively reduced depression, anxiety, and stress symptoms in CHD patients compared with the control group. CBT-based interventions improve patients' knowledge about CHD through psychological education, and the corresponding cognitive and behavioral techniques contribute to the changes in non-adaptive beliefs of patients[43]. As for CHD patients with depression symptoms, their negative thinking mode can be altered through cognitive reconstruction[44]. For anxiety and stress emotions, the excitability of sympathetic

Table 4 Subgroup analysis on the effect of cognitive behavioral therapy-based interventions on anxiety symptoms

Subgroups	Anxiety symptom: Post- to pre-treatment effect						
	Studies (*n*)	Participant (*n*)	I^2 % (*P* value)	*Q*-test	MD (95%CI)	SMD (95%CI)	*P* value (between)
Treatment form							0.100
Group	5	320	50 (0.090)	7.96	-1.24 (-2.63, 0.15)	-0.27 (-0.57, 0.04)	
Individual	8	913	94 (< 0.001)	123.83	-3.25 (-5.17, -1.32)[b]	-0.62 (-1.05, -0.18)[b]	
Treatment course							0.280
≥ 12 wk	8	935	73 (0.001)	25.76	-0.73 (-1.69, 0.23)	-0.16 (-0.40, 0.08)	
< 12 wk	5	261	90 (< 0.001)	38.38	-2.47 (-5.48, 0.54)	-0.63 (-1.37, 0.12)	
Duration of session							0.050
≥ 50 min	9	652	89 (< 0.001)	71.35	-2.49 (-4.88, -0.09)[a]	-0.43 (-0.86, -0.00)	
< 50 min	2	318	0 (0.540)	0.38	-0.12 (-0.35, 0.11)	-0.13 (-0.35, 0.09)	
Number of session							0.150
≥ 10	6	617	79 (0.000)	23.89	-0.98 (-2.77, 0.80)	-0.18 (-0.54, 0.18)	
< 10	7	458	92 (< 0.001)	70.66	-3.50 (-6.42, -0.58)[a]	-0.66 (-1.23, -0.10)[a]	
Treatment delivery way							0.390
Remote	4	383	94 (< 0.001)	51.28	-0.59 (-4.68, 3.51)	-0.29 (-1.17, 0.59)	
Face to face	10	910	90 (< 0.001)	88.49	-2.54 (-4.17, -0.90)[b]	-0.47 (-0.78, -0.16)[b]	
Manual available							0.200
Yes	4	214	50 (0.110)	6.03	-0.86 (-2.73, 1.02)	-0.19 (-0.52, 0.13)	
No	10	1079	93 (< 0.001)	135.85	-2.48 (-4.12, -0.84)[b]	-0.52 (-0.91, -0.12)[a]	
Psycho-education strategies							0.140
Important	10	1021	93 (< 0.001)	128.71	-2.71 (-4.29, -1.13)[c]	-0.57 (-0.95, -0.19)[b]	
Not important	4	272	77 (0.004)	13.30	-0.14 (-3.14, 2.86)	-0.03 (-0.54, 0.48)	
Behavioral strategies							0.003
Important	9	998	94 (< 0.001)	134.13	-3.46 (-5.33, -1.60)[c]	-0.67 (-1.07, -0.27)[b]	
Not important	5	295	47 (0.110)	7.57	0.13 (-1.27, 1.54)	0.05 (-0.26, 0.36)	
Cognitive strategies							0.020
Important	11	1102	93 (< 0.001)	134.22	-2.84 (-4.37, -1.31)[c]	-0.57 (-0.91, -0.22)[b]	
Not important	3	191	72 (0.030)	7.26	1.06 (-1.95, 4.06)	0.16 (-0.37, 0.69)	
Interpersonal strategies							0.190
Important	2	390	46 (0.180)	1.84	-0.59 (-2.50, 1.32)	-0.09 (-0.31, 0.13)	
Not important	12	903	92 (< 0.001)	140.01	-2.30 (-4.01, -0.59)[b]	-0.48 (-0.86, -0.10)[a]	
Body directed strategies							0.150
Important	5	694	67 (0.020)	12.22	-0.64 (-1.51, 0.22)	-0.19 (-0.43, 0.05)	
Not important	9	599	91 (< 0.001)	87.09	-2.73 (-5.43, -0.02)	-0.50 (-1.01, 0.00)	
Homework assignment strategies							0.640
Important	5	529	91 (< 0.001)	45.80	-2.60 (-5.42, 0.23)	-0.61 (-1.17, -0.04)[a]	
Not important	9	764	91 (< 0.001)	84.86	-1.79 (-3.62, 0.04)	-0.31 (-0.72, 0.09)	

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
MD: Mean difference; SMD: Standard mean difference; CI: Confidence interval.

Table 5 Egger's regression analysis on publication bias

Variables	T	*P* value	95%CI
Depression symptom	-0.75	0.467	-2.60, 1.25
Anxiety symptom	-1.37	0.196	-7.36, 1.68
Stress symptom	-4.42	0.021	-9.65, -1.57
BMI	-	-	-
Systolic pressure	0.78	0.516	-4.71, 6.80
Diastolic pressure	-0.24	0.836	-3.48, 3.12
Total cholesterol	-	-	-
HDL	-	-	-
Physical function	-0.23	0.829	-5.76, 4.83
Mental function	2.03	0.135	-3.83, 17.40
6-min walk distance	-	-	-

BMI: Body mass index; HDL: High-density lipoprotein; CI: Confidence interval.

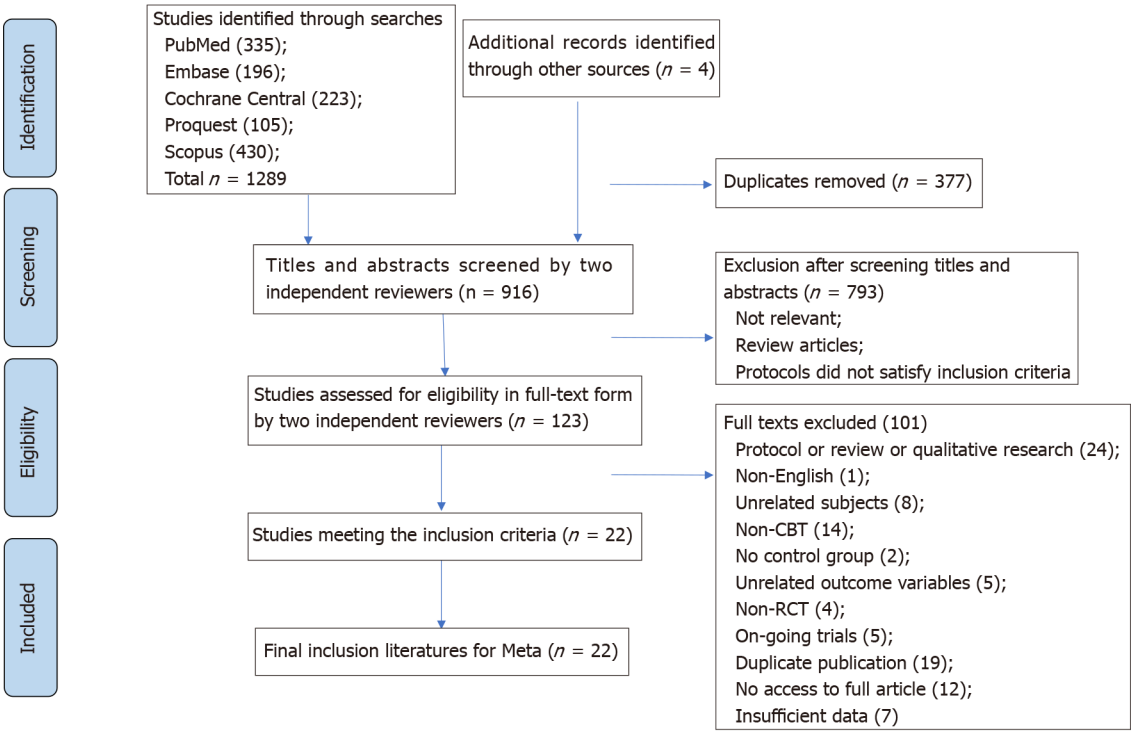


Figure 1 PRISMA flow diagram. CBT: Cognitive behavioral therapy; RCT: Randomized controlled trial.

nerves can be reduced through relaxation and behavioral techniques so that the mood can be improved[44].

We did subgroup analyses to found effective characteristics and components of CBT-based interventions in improving the symptoms of depression and anxiety in CHD patients. Firstly, CBT is more effective when it is provided as an individual rather than group treatment. The possible reason is that the individual treatment method is more targeted and more effective in treating the symptoms of depression and anxiety. Secondly, interventions that do not use a CHD-specific manual have a better effect on symptoms of depression and anxiety due possibly to the fact that the manual approach focuses more on the management of CHD rather than on negative emotions. This is consistent with the conclusions of research conducted by Yang *et al* [23] on diabetic patients. Thirdly, CBT is more efficient when it emphasizes psycho-

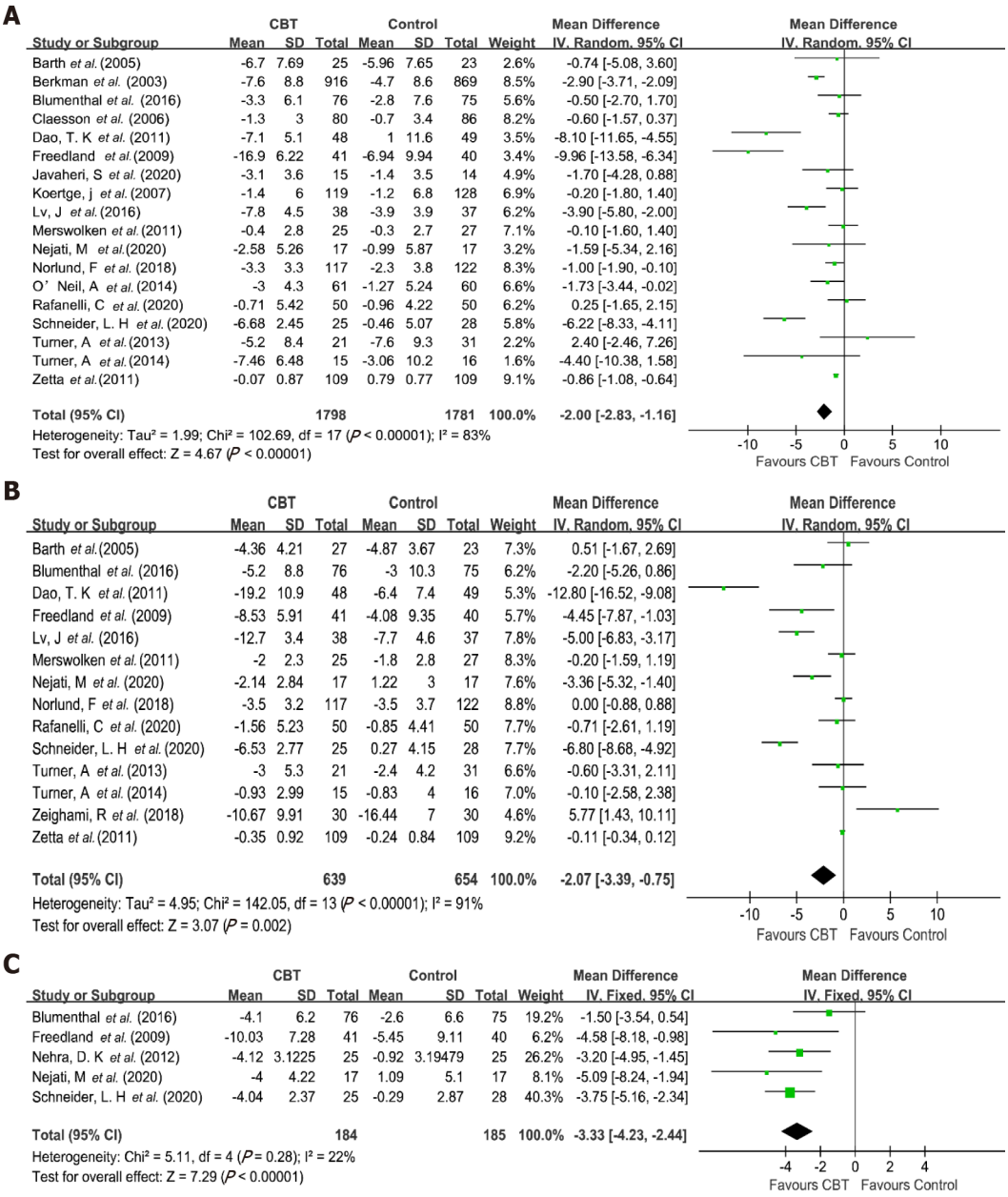


Figure 2 Forest plots of the effects of cognitive behavioral therapy-based interventions. A: Depression symptom; B: Anxiety symptom; C: Stress symptom. CBT: Cognitive behavioral therapy; CI: Confidence interval.

education, behavioral and cognitive strategies as the core approaches, consistent with previous research conclusions, indicating CBT should highlight these strategies as the core[38,39].

Effects on physiological factors: Our meta-analysis found that CBT-based interventions have a significant effect on the reduction of BMI. The possible reason is associated with the improvement of health-related behaviors. Zetta *et al*[42] undertook research to analyze the effect of CBT in patients with angina. The intervention group patients reported increased knowledge awareness, fewer misconceptions, and an increase in self-reported exercise. Murphy *et al*[37] found a significantly reduced dietary fat intake among intervention group patients, indicating the favorable impact of the CBT and motivational interviewing program on patient nutritional habits. Thus, CHD patients' knowledge of the disease and their behavior habits may be improved through CBT-based interventions. They are more likely to maintain a good diet and moderate physical exercise to achieve weight loss goals.

Previous studies have found that CBT-based interventions can help to improve blood pressure and lipid profiles by reducing physiological stress caused by negative emotions, improving autonomic nervous system and endocrine system function[45]. However, we did not find CBT was effective in improving participants' blood pressure

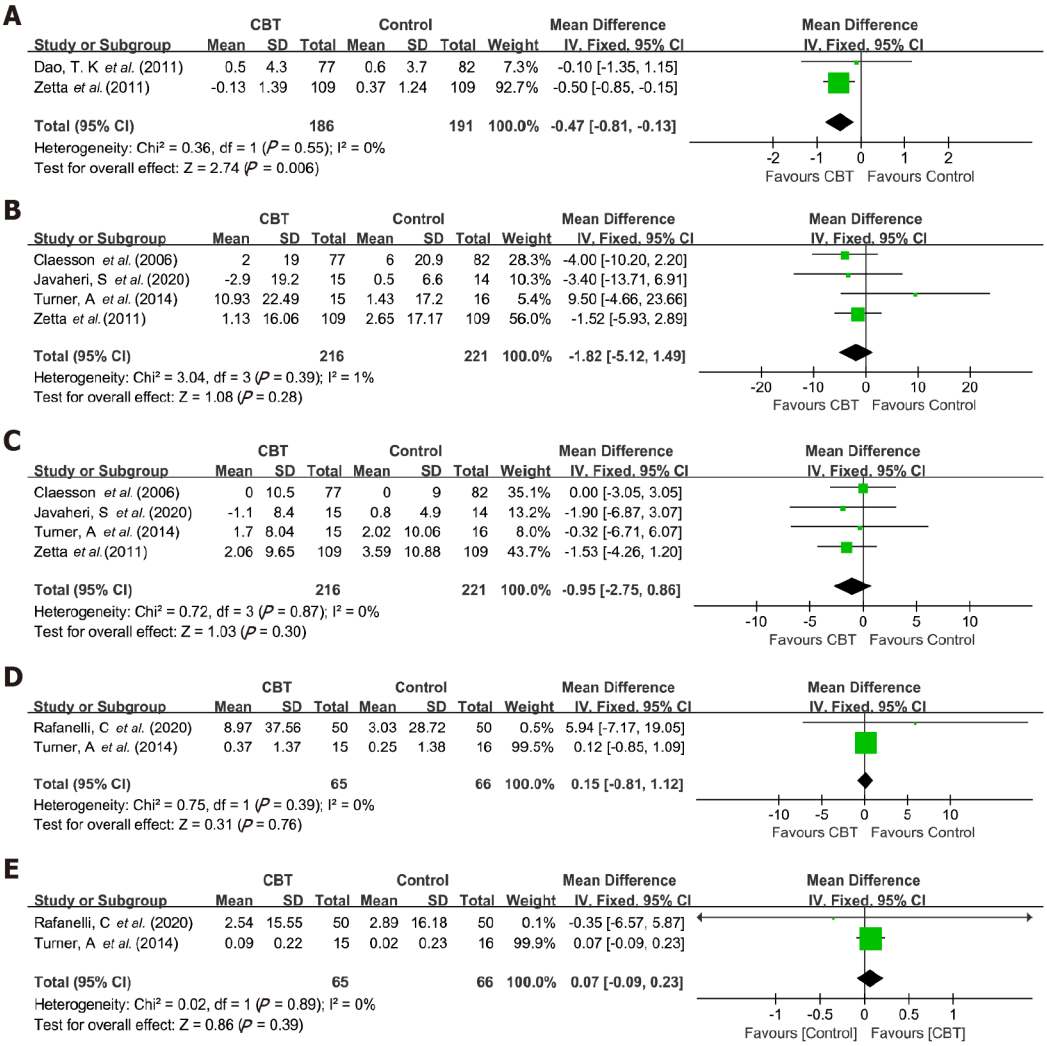


Figure 3 Forest plots of the effects of cognitive behavioral therapy-based interventions. A: Body mass index; B: Systolic blood pressure; C: Diastolic blood pressure; D: Total cholesterol; E: High-density lipoprotein cholesterol. CBT: Cognitive behavioral therapy; CI: Confidence interval.

and lipid profiles. The possible reason is that only four studies reported on blood pressure and two studies on blood lipids. Both blood pressure and blood lipids have complex metabolic mechanisms, reflecting the need for a more significant number of studies to be conducted to assess the effect of CBT-based intervention on these factors accurately.

Effects on QOL and exercise endurance: Increasingly, QOL has become the focus of disease treatment and rehabilitation[46]. In this study, seven studies reported physical function, and five reported mental function. We found that CBT-based interventions can effectively improve patients' physical and mental function, consistent with previous studies[40]. It is possible that through CBT, the patient's negative mood is altered, improving their psychological state. At the same time, through techniques, such as behavioral activation, the exercise time of patients is increased, which is conducive to physical health.

The 6-Minute Walk Test is used to measure functional capacity[47]. As physical function improves, the 6-minute walking distance becomes longer. In contrast with our expectation, we found that the 6-min walk distance of CHD patients was not statistically improved through a CBT intervention. A possible reason for this finding is that only two studies reported this outcome variable. The improvement of a 6-minute walking distance is a long-term, complex process. The size of our sample was insufficient to draw conclusions about any changes in functional capacity.

Strengths and limitations of the study

The advantage of this paper is that it included 22 studies of moderate to high quality. In addition, unlike previous research, this paper also conducted subgroup analyses to

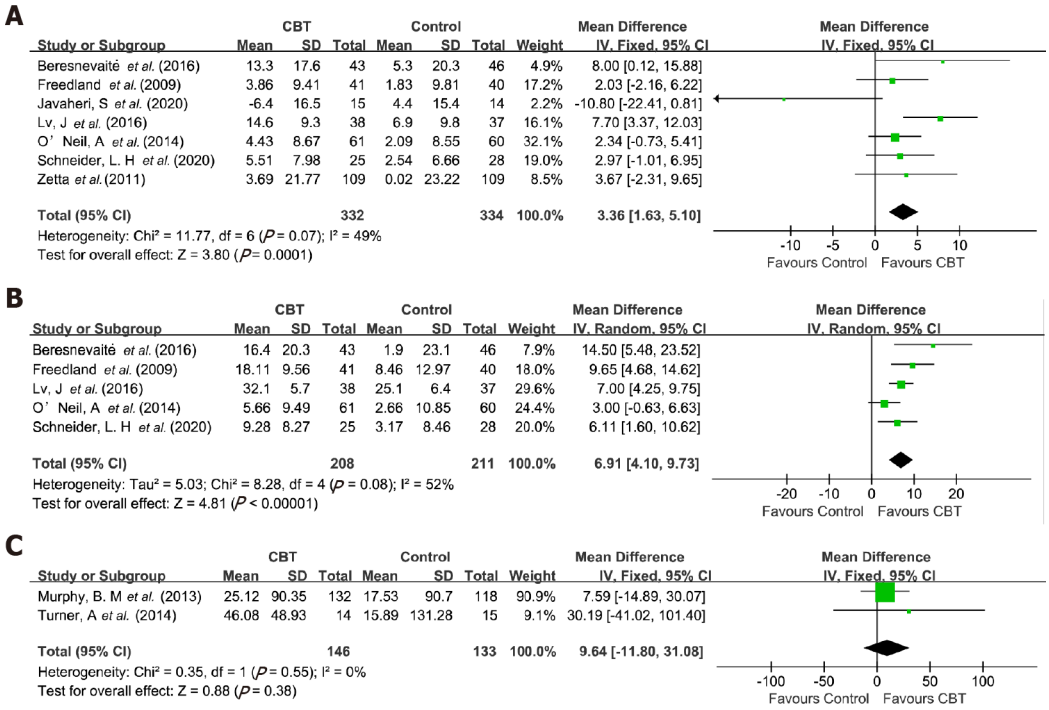


Figure 4 Forest plots of the effects of cognitive behavioral therapy-based interventions. A: Physical function; B: Mental function; C: 6-min walk distance. CBT: Cognitive behavioral therapy; CI: Confidence interval.

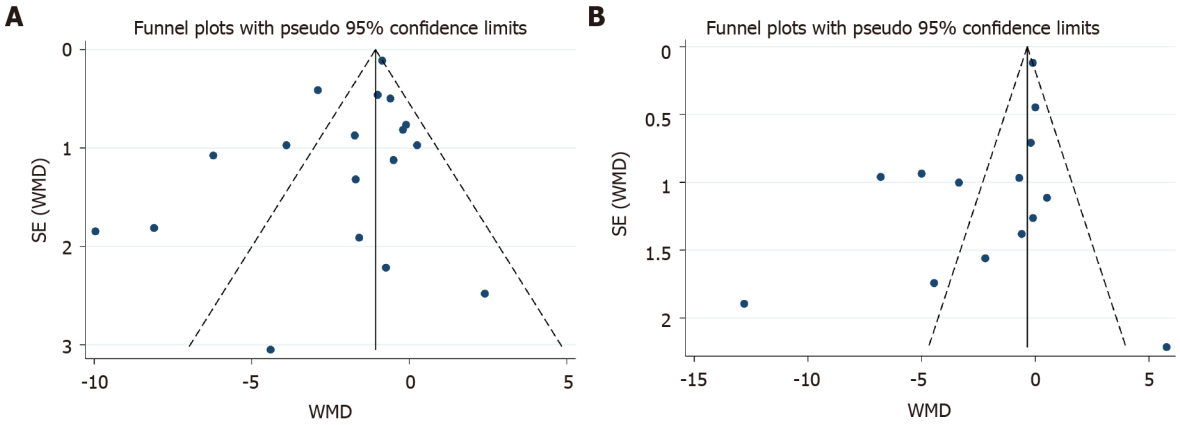


Figure 5 Funnel plots. A: Depression symptom; B: Anxiety symptom. WMD: Weighted mean difference.

explore specific characteristics of the CBT intervention, finding some critical components as described above. However, this paper also has some limitations. Due to the small number of articles included in the analysis, we must treat the results with some caution and conclude that more RCTs are needed to enhance the reliability of the evidence. Regarding other limitations, we only analyzed the results before and after the intervention and did not discuss the long-term follow-up results due to insufficient data. Therefore, there was a lack of long-term intervention effects of CBT-based interventions on CHD patients. Secondly, some studies were not able to use a double-blinded study design due to ethical reasons. Consequently, the quality of some of the evidence in this study may be not high. Thirdly, due to the limited number of studies reporting physiological factors, we need to be cautious in concluding the impact of CBT on these factors. Fourth, only articles written in English were included. Hence, it is possible that many eligible studies written in other languages were missed.

Implications

An increasing number of studies have applied CBT-based interventions to manage chronic pain[48], hypertension[49], diabetes[50], and cancer[51] and have found CBT interventions have been effective in improving health outcomes in these patients.

Similarly, our meta-analysis found a positive impact of CBT-based interventions on psychological and physiological factors and QOL in patients with CHD. It is, therefore, reasonable to speculate that the use of CBT as a CHD rehabilitation program is effective. CBT can be incorporated into such programs in hospitals or communities. However, given there has been no standardized procedure for CBT-based interventions for CHD until now, it is advisable to infer that the regular supervision of experienced psychotherapists and psychologists is indispensable to guarantee the quality of CBT delivery.

CONCLUSION

This systematic review and meta-analysis findings suggest that CBT-based intervention is effective for CHD patients in reducing symptoms of depression, anxiety, and stress, BMI levels, and improving physical and mental functioning. In addition, the intervention may be more effective for depression and anxiety in CHD patients when it is delivered as an individual treatment method, when there is no CHD-specific manual, and psycho-education, behavioral, and cognitive strategies are applied as the main approaches.

ARTICLE HIGHLIGHTS

Research background

Coronary heart disease (CHD) is the most common coronary atherosclerotic heart disease, leading to adverse health outcomes for patients with CHD. Cognitive behavioral therapy (CBT) is a short-term psychotherapy, which has been increasingly recognized as an effective intervention approach to reduce psychosocial risk factors in CHD patients. CBT is to change an individual's non-adaptive thought patterns and beliefs, leading to positive behavioral changes. However, no comprehensive systematic review has been conducted to evaluate the efficacy of the CBT-based intervention on health outcomes in patients with CHD.

Research motivation

There is an increasing number of randomized control trials to investigate the efficacy of the CBT-based intervention in CHD patients. However, no comprehensive systematic review has been conducted, and there has been no meta-analysis of the effects of key components of CBT on health outcomes in patients with CHD.

Research objectives

This study aimed to synthesize results from previous randomized controlled trials (RCTs) using a meta-analysis method and explore the therapeutic effect of CBT-based intervention on health outcomes in CHD patients. The secondary aim was to analyze several key components of CBT interventions that explained the effects of CBT intervention.

Research methods

Relevant RCTs published in English were obtained by searching PubMed, Embase, Cochrane Central Register of Controlled Trials, Scopus, and Proquest, with the retrieval time from inception to August 2020. Review Manager 5.3 was used to conduct the meta-analysis. We used The Physiotherapy Evidence Database tool to assess the quality of included studies. Mean difference (MD) was used for continuous outcome variables, and standardized MD was used to measure the effect size. The random-effect model was used to estimate outcomes based on the heterogeneity testing. I^2 was used for heterogeneity testing, and Egger regression was used to assess the publication bias.

Research results

A total of 22 RCTs were included in the systematic review and meta-analysis. The primary analysis revealed that CBT-based intervention significantly reduced depression, anxiety, stress symptoms, and body mass index (BMI) levels, and improved physical and mental functioning of the quality of life. Additionally, subgroup analysis found that CBT-based interventions were particularly effective in

reducing symptoms of depression and anxiety in CHD patients when individual treatment form was used, and when psycho-education, behavioral and cognitive strategies were applied as the core treatment components.

Research conclusions

CBT-based interventions are effective in improving health outcomes in CHD patients, including reducing depression, anxiety, stress symptoms, BMI levels, and improving quality of life. Subgroup analysis further found CBT was more effective in reducing depression and anxiety symptoms in CHD patients when it is an individual treatment method, and when psycho-education, behavioral and cognitive strategies are emphasized as the core intervention strategies.

Research perspectives

Our research findings suggest that CBT is a promising approach in the health promotion of the population with CHD. However, the current practice in CBT-based interventions for CHD is not standardized, therefore, further research to standardize the CBT approach in clinical and community intervention programs in patients with CHD is needed.

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ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 December 19; 11(12): 1167-1424



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Monthly Volume 11 Number 12 December 19, 2021

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INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xu Guo*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
December 19, 2021

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INSTRUCTIONS TO AUTHORS
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STEPS FOR SUBMITTING MANUSCRIPTS
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ONLINE SUBMISSION
https://www.f6publishing.com

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E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1167-1176

DOI: 10.5498/wjp.v11.i12.1167

ISSN 2220-3206 (online)

EVIDENCE REVIEW

Child abuse and psychopathy: Interplay, gender differences and biological correlates

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Author contributions: Santorelli M and di Giacomo E wrote this manuscript; Rucco D, Colmegna C, Pessina R, Placenti V, Aliberti F and Clerici M collected data; All authors analyzed papers and approved the final version of the manuscript.

Conflict-of-interest statement: No conflict of interest to disclose.

Country/Territory of origin: Italy

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

Child abuse is an important source of mental and physical adverse consequences for victims, their family, and their community. The impact of violence during childhood on the development of the victim is a very sensitive theme. Other than internalizing symptoms, it is interesting to analyze the possibility that a victim may assume the role of persecutor. With this aim, we evaluate Literature and examine the interplay among different types of child abuse (emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse) and the development of psychopathy. We consider the role of post-traumatic stress disorder and that of personal environment as potential mediators between abuse and psychopathy. Furthermore, an in-depth analysis on possible differences due to the victim's gender is performed. Finally, analysis focused on genetic variants, such as the polymorphism of 5HTT and MAO-A, or a biological alteration, like the difference in daily cortisol levels that could be related to the development of psychopathy after a trauma.

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Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: May 13, 2021
Revised: May 27, 2021
Accepted: November 18, 2021
Article in press: November 18, 2021
Published online: December 19, 2021

P-Reviewer: Conde D
S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL



Key Words: Child abuse; Sexual abuse; Physical abuse; Psychopathy; Neglect; Intergenerational transmission

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Core Tip: Childhood trauma and psychopathy are strictly related; emotional abuse, emotional neglect and physical abuse show stronger association with the development of psychopathy. Even if sexual abuse is more frequent in females, most researches did not find a significant correlation between psychopathy and sexual abuse in both genders. Furthermore, trauma is the hallmark of secondary psychopathy causing, in a fragile mind, the uprising of mental illness.

Citation: di Giacomo E, Santorelli M, Pessina R, Rucco D, Placenti V, Aliberti F, Colmegna F, Clerici M. Child abuse and psychopathy: Interplay, gender differences and biological correlates. *World J Psychiatr* 2021; 11(12): 1167-1176
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1167.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1167

INTRODUCTION

Child abuse is a strong predictor of short and long term physical and mental illness. Five types of maltreatment are commonly recognized: Sexual, physical and emotional abuses (EAs) and physical and emotional neglect. Child sexual abuse is a serious concern with worldwide prevalence rates between 8%-31% for girls and 3%-17% for boys[1]. Every year, about 4%-16% of children are physically abused and one in ten is neglected or psychologically abused. During childhood, between 5% and 10% of girls and up to 5% of boys are exposed to penetrative sexual abuse, and up to three times higher numbers of children are exposed to any kind of sexual abuse[2].

Many research findings support the hypothesis that exposure to early life stress in the form of child abuse and/or neglect is associated with a huge increased vulnerability to major psychiatric and other medical disorders[3]. Research shows that children who have been physically or sexually abused have a greater risk of depression, suicidality, post-traumatic stress disorder, as well as antisocial personality disorder, psychopathic traits or psychopathy. Psychopathy is characterized by distinct interpersonal and affective traits (*e.g.*, manipulativeness, callousness), as well as a disinhibited, reckless lifestyle (*e.g.*, impulsivity, irresponsibility)[4].

The aim of the present narrative review is to evaluate the interplay between child abuse and psychopathy with special attention to gender differences and possible biological causes.

PRIMARY AND SECONDARY PSYCHOPATHY

An original theory differentiates the psychopathy in two subcategories: Primary psychopathy that have innate biological origins and could be characterized by low levels of anxiety and secondary psychopathy developed in response to adverse environmental experiences (Table 1). Primary psychopaths are incapable of emotions such as empathy and guilt, and so appear callous, cold, and lacking anxiety. In contrast, secondary psychopaths have a relatively normal capacity for emotional experience. Due to environmental stressors and trauma, however, they experience an excess of negative emotions and so exhibit high levels of anxiety and emotional distress, hostility, aggression, and impulsive behavior. Those differences would mirror the characteristics of the Psychopathy Checklist-Revised - PCL-R Factor 1 (F1; interpersonal and affective traits) and Factor 2 (F2; impulsive, antisocial, and chronically unstable lifestyle).

Dargis *et al*[5] studied the correlation between primary and secondary psychopathy (PCL:R) and trauma (Childhood Trauma Questionnaire-CTQ) in a sample of 110 psychopaths (PCL-R > 30) *vs* 112 inmates (PCL-R < 30). The psychopaths were split in 2 subgroups: Low negative affect (LN, n = 72) and high negative affect (HN, n = 38).

Table 1 Primary and secondary psychopathy

Ref.	Sample (women, %)	Tests	Significant association
Borja and Ostrosky[7], 2013	194 (0)	ETI - PCL-R	EA, SA (HP *vs* LP) and PA (HP, MP *vs* LP)
Craparo *et al*[13], 2013	22 (0)	TEC - PCL-R	Total score (early exposure)
Dargis *et al*[9], 2017	183 (0)	CTQ - PCL-R	Total score, EA, EN, PA and PN
Dargis *et al*[5], 2018	222 (0)	CTQ - PCL-R	Total score, EA, EN, PA, PN (HN); PA and PN (LH)
Gobin *et al*[11], 2015	88 (57.95)	CTQ - PPI	PA
Kolla *et al*[10], 2013	45 (0)	ETI - PCL-R	PA
Ometto *et al*[8], 2016	107 (43.92)	CTQ - PCL:YV	Total score, EN and PA
Poythress *et al*[15], 2006	615 (0)	CATS - PPI	Total score
Schimmenti *et al*[6], 2015	78 (0)	TEC - PCL-R	EA and PA (only to factor 2)
Schraft *et al*[14], 2013	170 (15.64)	CTQ - PCL:YV	Total score, EA, EN, PN
Woodfield *et al*[12], 2016	101 (0)	LEC-5 - SRP-SF	Total score

HN: High negative affect; LN: Low negative affect; LP: Low psychopathy levels; MP: Medium psychopathy level; HP: High psychopathy level; PA: Physical abuse; EN: Emotional neglect.

The HN subgroup scored significantly higher at the CTQ total score than the LN subgroup. In particular, the HN subgroup scored significantly higher in EA, PA, EN; while they did not differ for PN and SA. HN psychopaths scored higher than the other inmates at the CTQ total score and in all types of abuse except for SA. LN psychopaths significantly suffered more PA and PN than other inmates. The hallmark of the difference between secondary psychopathy (HN) and primary psychopathy (LN) was emotional neglect and EA that were significantly higher in HN compared to LN offenders suggesting that emotional maltreatment has specific associations with that subtype of psychopathy.

Schimmenti *et al*[6] evaluated the link between child abuse (CA) (measured with the Traumatic Experiences Checklist-TEC) and psychopathy (measured with Psychopathy Checklist-Revised - PCL-R) in 78 male prisoners. The EA was significantly related to the PCL-R total score, factor 1 (interpersonal/affective facets) and factor 2 (lifestyle/antisocial facets); while Physical abuse (PA) was linked only to factor 2. Furthermore PCL-R total scores were higher when EA occurred in childhood. As a consequence, the authors hypothesized a key role of EA in childhood; in fact, it was the best predictor of psychopathy scores and could distort the affective development of children, as implied in the construct of malignant narcissism, which has been theoretically proposed as a crucial dimension for understanding the inflated self-representation and lack of empathy among criminals.

Similarly, Borja *et al*[7] evaluated the relationship between several early traumatic events and psychopathy analyzing 194 male inmates with the PCL-R and the Early Trauma Inventory (ETI). They divided inmates in 3 subgroups: Those with low psychopathic levels (LP, n = 96, scoring 0-19 point at the PCL-R); inmates with medium psychopathy level (MP, n = 59, scoring from 20 to 29) and inmates with a high level of psychopathy (HP, n = 44, scores > 30). EA and SA were significantly higher in HP compared to LP group. Moreover PA was higher in MP *vs* LP and HP *vs* LP. After a regression analysis they found that early-life traumatic events and EA strongly influenced the PCL-R total score. Additionally HP and MP were exposed to more hostile environment than LP. Ometto and colleagues[8] underlined the relationship between abuse, detected through the CTQ, and the development of psychopathy (Psychopathy Checklist:Youth Version; PCL:YV) in 107 teenagers. The PCL:YV total score was positively correlated to the abuse and inversely correlated to the frequency of general social skill (measured with The Multidimensional Personality Questionnaire-Brief Form [MPQ-BF]). In the same study, Emotional neglect (EN) was positively related to the PCL:YV total factor and interpersonal, affective and lifestyle factors. PA was positively correlated to the PCL:YV total factor and affective, lifestyle and antisocial factors of the PCL:YV. Emotional and sexual abuse were not related to psychopathy. At a Multiple linear regression for the association of distinct types of maltreatment (CTQ) and social skills (Social Skills Inventory for Adolescents; SSIA) with psychopathic features (PCL: YV), EN was the only abuse related to psychopathy,

especially with the interpersonal Factor.

Dargis *et al*[9] examined psychopathy (PCL:R) and trauma (CTQ) in 183 inmates and discovered a significant correlation between the CTQ total score and Psychopathy, in particular PA, PN, EN and EA were significantly related to the PCL:R but no significant relation with SA was found. Factor 2 (lifestyle and antisocial features load) was related to the CTQ total score while EA, EN, PA and Factor 4 (antisocial features) were related to PA and CTQ total score; no link between factor 1 and trauma was detected. Dargis and colleagues evaluated Antisocial Personality Disorder (ASPD), trauma and Conduct Disorder (CD): PA was the only form of trauma related to ASPD while CD was related exclusively to SA. With the same aim, Kolla *et al*[10] evaluated the link among ASPD, psychopathy (PCL-R) and trauma in 45 subjects divided in 3 subgroups: 10 inmates with ASPD and psychopathy (PCL-R > 25), 15 ASPD without psychopathy (PCL-R < 25) and 15 non offenders. The first group reported greater physical abuse during childhood but no more sexual or EAs than those without psychopathy.

THE IMPACT OF POST TRAUMATIC STRESS DISORDER

Another important variable that deserves consideration is the role of PTSD in the interplay between trauma and psychopathy; the work of Gobin *et al*[11] analyzed this variable in 88 inmates (51 females and 37 males) evaluating ASPD (Structured Clinical Interview for DSM Axis II Personality Disorders; SCID-II), trauma (CTQ), psychopathy (Psychopathic personality inventory; PPI) and PTSD (PTSD checklist civilian version). Physical and crime-related trauma were associated with ASPD, while sexual abuse was not. Victims of PA were 5.04 times more likely to be diagnosed with ASPD than those without history of PA. Likewise, inmates with history of crime related trauma were 2.92 more likely to be diagnosed with ASPD than those without. PA was confirmed as the only type of trauma related to psychopathy, whereas the severity of PTSD symptoms was not related to the PPI or ASPD. The role of PTSD was also examined by Woodfield *et al*[12] They underlined a relation between psychopathy (Self-report psychopathy scale-short Form; SRP-SF), trauma (The life events checklist; LEC-5) and PTSD (The Posttraumatic Stress Disorder-checklist Version 5). The total LEC-5 score was significantly related to both primary and secondary factors, but the secondary had a stronger correlation with trauma. More importantly, only the secondary facet of psychopathy had a correlation with PTSD, showing a key role in moderating the effect of trauma on the development of PTSD. Specifically, trauma exposure was positively associated with increased PTSD symptoms in individuals with low levels of secondary psychopathy, and negatively associated with PTSD symptoms with those with high levels of secondary psychopathy. These findings contribute to the understanding of the nature of the relationships between PTSD, psychopathic facets, and trauma exposure, as the association between trauma exposure and PTSD is explained by secondary but not primary psychopathic traits.

Craparo *et al*[13] examined the role of age in mediating the effect of trauma on the development of psychopathy. They measured traumatic experiences (TEC) and traits of psychopathy (PCL-R) in 22 male subjects and suggested that an early exposure to relational trauma in childhood can play a relevant role in the development of more severe psychopathic traits. Indeed, subjects with higher PCL-R score experienced relational traumatic events earlier in life compared to the rest of participants. There was also a significant negative association between age at first relational trauma and psychopathy scores.

THE ROLE OF COMMUNITY VIOLENCE

Another variable that needs to be taken in consideration is the role of violence in the community in the relationship between trauma and psychopathy.

Schraft *et al*[14] highlighted the effect of community violence (Community Experience Questionnaire; CEQ) on trauma (CTQ) and psychopathy (PCL:YV) in their work on 170 detained adolescents (147 males, 23 females). The CTQ total score was positively correlated to the PCL:YV total score and scores of the PCL:YV behavioral and antisocial factors. The CEQ total score positively correlated to the PCL:YV total scores, as well as to scores of interpersonal, behavioral, and antisocial factors. EA, PN and EN were associated with higher levels of psychopathic traits. Higher levels of traumatic exposure within home and community were associated with higher levels of

psychopathic characteristics. Higher CEQ scores were related to higher scores in behavioral and antisocial facets of psychopathy.

PSYCHOPATHY, TRAUMA AND DISSOCIATION

Poythress *et al*[15] evaluated the role of Dissociative experiences (Dissociative experiences scale; DES) in the link between trauma (Child abuse and Trauma Scale; CATS) and psychopathy in 615 male inmates**.** Psychopathy, abuse, and dissociation scales were weakly but significantly associated one with another. Tests of correlation revealed that the lifestyle features of psychopathy were significantly more linked to abuse total scores than affective or interpersonal features. Furthermore, lifestyle feature of psychopathy was significantly more correlated to the DES total score than interpersonal features, but not to affective ones. Abuse was not related to interpersonal and affective features of psychopathy. In contrast, abuse exerted a direct effect on impulsive and irresponsible lifestyle, and that relationship was not mediated by dissociative experiences. Their research demonstrated that child abuse is positively linked, even if weakly, to psychopathy and moderately to the impulsive and irresponsible lifestyle of psychopaths without a significant mediation of dissociative symptoms.

BIOLOGICAL CORRELATES

Different studies analyzed the role of biological alterations that may link trauma and psychopathy (Table 2). Cima and colleagues[16] evaluated variations of salivary cortisol in 47 (24 psychopath and 21 non psychopath) inmates tested with the PPI scale for psychopathy, the CTQ for childhood trauma, compared to the group of non-psychopaths -control group (27 males). The salivary cortisol was analyzed four times a day at 8 am, 11am, 2pm and 4pm. Criminals, non-psychopathic as well as psychopathic, reported significantly more traumatic childhood experiences than the control group and the non-psychopathic criminals did not differ from psychopathic criminals except for PN, which difference was significant. Trauma and salivary cortisol were not related in the whole sample.

Nevertheless, they found a reduction on the Daily Average Cortisol (DAC) in psychopaths that was also significantly related to PA. Besides, the cortisol area under the curve (AUC) in that group was related to EA and EN, the diurnal cortisol slope was related to PN with a significant relation between the PPI total score and DAC. Traumatic experiences, in that group, was also positively related to impulsive nonplanfullness (fourth subscale of the PPI) and external blame attribution factor on the PPI, while there was a negative association between traumatic childhood experiences, cold-heartedness and stress immunity. The crucial finding of this study was the evidence of hypoarousal in psychopaths with a reduction of the diurnal cortisol compared to non-psychopaths. This finding fits with the notion that non-psychopathic offenders are more reactive, emotional delinquents, while psychopathic offenders are more instrumental and cold-blooded.

Two studies analyzed monoamine oxidase-A (MAO-A) and 5-hydroxyindoleacetic acid transporter (5HTT) alterations in connection to psychopathy and trauma. Sadeh *et al*[17] analyzed 237 inmates with the CTQ and the PCL:SV, and their genetic variations of 5HTT and MAO-A were detected from saliva samples. The PCL:SV factor 1 (interpersonal/affective facets) was higher in 5HTT long/Long allele *vs* short/short, but it was not found an etiological explanation linking trauma, psychopathy and genetic alterations. The PCL:SV factor 2 (lifestyle/antisocial facets) was higher in people with the MAO-A variant with low activity *vs* high activity moreover 5HTT long/Long have higher PCL:SV factor 2 than short/short. In particular MAO-A genotype was most consistently associated with the impulsive and irresponsible traits of the Lifestyle factor. Interestingly, no correlation was found between genetic alteration and the trauma-psychopathy link. Likewise, in the work of Hollebarch *et al* [18], which evaluated trauma (CTQ), psychopathy (Self-Reported Psychopathy scale) and the MAO-A uVNTR genotype in a sample of 2796 people, MAO-A uVNTR genotype was significantly associated to general psychopathy in women, meaning that women with the MAOA-L genotype had slightly higher levels of psychopathy compared to their MAOA-H counterparts, but they did not find the same in men. Childhood trauma was associated with psychopathic traits in adults, both in men and women. They did not find any interaction between MAOA uVNTR genotype and any

Table 2 Different studies analyzed the role of biological alterations that may link trauma and psychopathy

Ref.	Sample (women, %)	Tests	Significant association	Biological analysis
Cima *et al*[16], 2008	47 (0)	CTQ - PPI	PN (Psychopath *vs* inmates not psychopath)	DAC (related to PN) reduction in psychopath; AUC related to EA, EN
Hollerbach *et al*[18], 2018	2796 (45.24)	CTQ- SRPS	Total score	Total score in women (MAOA-L); MAOA-L in women related to EA, EN and PN
Sadeh *et al*[17], 2013	237 (0)	CTQ-PCL:SV	NS	F1 (5HTT long/long *vs* 5HTT short/short; F2 (MAOA-L *vs* MAOA-H)

DAC: Daily average cortisol; AUC: Cortisol area under curve; F1: Factor 1 of PCL:SV; F2: Factor 2 of PCL:SV; MAOA-L: MAO-A low activity; MAOA-H: MAO-A high activity.

traumatic factor on psychopathic traits. Their results suggest that psychopathy in general, and social deviance in particular, were associated with childhood trauma in men and women, and that psychopathic traits are subject to variation of the MAOA uVNTR genotype in women. Hollebarch and colleagues[18] discovered that the "childhood trauma" factor was not influenced by a variation of MAO-A in men, while women with MAOA-H genotype showed a slightly higher scores of PN, EN and EA. In general, no significant link that could explain the influence of trauma on psychopathy has been discovered yet. We could explain this result with the primary and secondary psychopathy theory, according to which the primary psychopathy has a genetic cause that determines the onset of the illness whereas the secondary psychopathy has traumatic and problematic environmental reasons as etiological causes. Further genetic study might explain the role of the genetic alterations that support the onset of psychopathy.

GENDER DIFFERENCES IN THE RELATIONSHIP BETWEEN TRAUMA AND PSYCHOPATHY

Watts *et al*[19] analyzed trauma (CTQ) and psychopathy (Levenson self-report psychopathy scale) in a non-forensic sample of 1169 subjects (73% female) (Table 3). They underlined two gender differences: the first one was the relation between boldness and childhood neglect that was negative or small to moderate in males but almost absent in females. The second was the relation between disinhibition, meanness and childhood maltreatment that was stronger for males than females. In their sample, men suffered more child abuse than women with the exception of sexual and EAs that were more frequent in females.

Thomson and colleagues[20] evaluated the role of sex differences in the association between the 4-facet model of psychopathy (PCL-SV) (interpersonal, affective, lifestyle, antisocial) and aggression (physical, verbal, and indirect), and LPA (Lifetime Physical Abuse) in a sample of 369 males and 204 females. The relation between physical aggression and affective facet of psychopathy was significant in both genders. High affective traits predicted physical aggression in women with a history of physical abuse but not in women without it. Instead, physical aggression was predicted by low affective traits in men with a history of physical abuse while lower levels of physical aggression were associated with low affective traits in men without a history of physical abuse. Moreover, verbal aggression was significantly related to the antisocial factor of psychopathy in women. Furthermore, high antisocial traits predicted verbal aggression exclusively in men who suffered from physical abuse.

Gender differences were also analyzed by Sevecke *et al*[21]. They studied 170 male and 171 female adolescent detainees using the CTQ, the PCL-YV and the Dimensional Assessment of Personality Pathology Basic Questionnaire (DAPP-BQ) for personality assessment. They found that gender was a strong predictor of the PCL:YV total score and all four psychopathy dimensions; incarcerated male adolescents had a significantly higher PCL:YV total score as well as all four psychopathy dimensions than incarcerated female adolescents. The PA was related to the antisocial facet of the PCL-YV in both males and females and it was also related to the interpersonal facet in males. No relation was found between SA and psychopathy in both genders. Interestingly, the subjects who did not suffer from PA had a stronger association

Table 3 Trauma and psychopathy in a non-forensic sample of 1169 subjects

Ref.	Sample (women, %)	Tests	Significant association in men	Significant association in women
Blonigen *et al*[25], 2012	226 (100)	PTE-PCL-R	/	Total score (AF)
Farina *et al*[24], 2018	976(19.98); P:253 (45); M:723 (13)	MAYSI-2+ CTQ- YPI +PPI-SF	PA, EA	PA, EA
Hicks *et al*[26], 2011	140 (100); 31 Pr, 39 Sc	I-PCL-R	/	PA (Sc); SA (Pr[19])
Krischer *et al*[23], 2008	283 (47.43)	CTQ- PCL:YV	PA (total score, AFC and AF); EA (AF)	EN (related with AF)
Lansing *et al*[22], 2018	107 (52.23)	CTQ- YPI	NS	EA
Sevecke *et al*[21], 2016	341(50.14)	CTQ - PCL:YV	PA (related to AF and IF)	PA (related to AF)
Thomson *et al*[20], 2019	573 (35.60)	LPA + AQ - PCL-SV	PAG (affective facet of psychopathy); LAT related to PAG in history of PA	PAG (related to AF); HAT related to PAG; in history of PA; VA[4] (related to ANF[5])
Watts *et al*[19], 2017	1169 (73)	CTQ - LPS	Child abuse (more frequent in male)	EA, SA (more frequent in female)

LPS: Levenson self-report psychopathy scale; HAT: High affective trait; PAG: Physical aggression; VA: Verbal aggression; ANF: Antisocial factor of psychopathy; LPA: Lifetime physical abuse; AQ: Aggression questionnaire; LAT: Low affective trait; AF: Antisocial factor of psychopathy; IF: Interpersonal factor of psychopathy; YPI: Youth Psychopathic Trait Inventory; AFC: Affective factor of psychopathy; MAYSI-2: Youth Screening Instrument Version 2 Traumatic Experiences Scale; PPI-SF: Psychopathic Personality Inventory-Short Form; P: Pennsylvania; M: Missouri; PTE: Potentially traumatic events; I: Interview, interview, prison file, and responses on the life events checklis; Pr: Primary psychopaths; Sc: Secondary psychopaths.

between emotional dysregulation and psychopathy than those who reported PA. Opposite to the study of Sveiche *et al* (no reference), Lansing *et al*[22] did not find any significant difference on the psychopathy scale in males compared to females. Women had higher frequencies of emotional and sexual abuse than men. In particular EA was the most frequent abuse for EOPD (Early onset persistent delinquent) girls while PA was the most common abuse among EOPD boys. Nearly half of the girls in their sample suffered from SA which was infrequently reported by boys. A significant correlation between psychopathy and abuse was documented only in women and it resulted particularly strong with EA. Lansing and colleagues supported a lack of significant relation between psychopathy and SA in men, and between PA and psychopathy in women. Kricher and colleagues[23] examined 185 adolescent inmates *vs* 98 students (control group) and discovered that abuse was more frequent among inmates than in the control group; women, in particular, reported significantly more emotional, sexual and physical abuses than men. Contrasting with previous studies, neither the PCL: YV total score, or any of its four factors significantly differed between abused and non-abused women except for the Factor 4 (antisocial psychopathy) that significantly correlated to Emotional Neglect in delinquent girls. Instead, boys that suffered PA had higher PCL-YV total scores as well as higher Affective and Antisocial Factors. Furthermore, they showed poorer Anger Control, more Irresponsibility and more Serious Criminal Behavior. Likewise, boys who reported EA were also characterized by significantly higher scores in the Antisocial Factor of the PCL-YV. Authors discovered a significant correlation between the Affective Factor 2 and Physical Abuse and between the Interpersonal Factor 1 of the PCL-YV and Emotional Neglect in male inmates. In contrast with Kricher *et al*[24], Farina and colleagues found a significant relation between trauma and psychopathy in both males and females. Their sample was recruited in 2 different penitentiaries: 253 inmates from Pennsylvania and 723 in Missouri, tested with the YPI and PPI-SF scale for psychopathy and the CTQ for trauma. In the Pennsylvania sample they found significantly more SA and EA in females than in males. Psychopathy was associated with physical and EAs in both male and female juvenile offenders with stronger association in girls. No correlation was found between SA and psychopathy in both genders. Another important variable they evaluated was the impact of PTSD in the relation between trauma and psychopathy in males and females. Blonigen *et al*[25] considered a sample of inmate women (26 of whom had a PCL-R > 30). Interpersonal and affective facets of psychopathy were unrelated to Potentially traumatic events (PET) or PTSD. Instead, they found a significant relation among antisocial facet and PET; furthermore, antisocial facet was uniquely associated with PTSD too. The lifestyle facet was prefer-

entially linked to abuse in adulthood and antisocial facet to abuse in childhood. Moreover, both PTE and PTSD were related to the factor 2 of psychopathy, known as the externalizing spectrum of psychopathy. The theory of primary and secondary psychopathy was also investigated in the study of Hicks *et al*[26] They evaluated psychopathy (PCL-R) with a different cut off (25), splitting the sample in 2 groups: 70 psychopaths and 70 controls. Out of 70 psychopaths, 31 were primary and 39 were secondary psychopaths. The secondary psychopaths had personality traits of negative emotionality and low behavioral constraint, more substance use disorder, more violent behavior and more mental health problems including symptoms of post-traumatic stress disorder and suicide attempts than primary psychopaths. The secondary psychopaths suffered more PA than controls prisoners or primary psychopaths. Instead, primary psychopaths experienced significantly more SA than controls. Moreover, secondary psychopaths reported significantly more PTSD symptoms, history of mental health treatments and suicidal attempts than control or primary psychopaths. An interesting finding was that primary psychopaths had lower rates of suicide attempts, though those rates did not differ significantly from that of control prisoners.

DISCUSSION

Child abuse is a serious public concern with adverse short and long term consequences. The aim of the present narrative review is the identification of the development of psychopathic traits in victims, with a special attention to gender differences and biological reasons.

Primary psychopaths, who are those characterized by a low level of anxiety and lack of emotions and sense of guilt, suffer less emotional maltreatments than secondary psychopaths, thus confirming the development of that subtype of psychopathy (secondary) in response to adverse experiences. In accordance, EA and neglect are related to affective facet with higher level of psychopathy at the PCL-R if EA occurs during childhood.

The severity of psychopathy is also linked to the moment of exposure to relational trauma with more serious traits in case of early exposure during childhood. Traumatic exposure to domestic violence or violence in the community is linked to higher degrees of psychopathy. Dissociative symptoms as well as post-traumatic stress disorder demonstrate weak association in the development of psychopathy after a childhood trauma. Similarly, biological correlates that could justify the development of psychopathy in response to traumatic experiences have not been demonstrated yet, even if women show a variation in the MAOA uVNTR genotype might be associated with psychopathic traits in victims of childhood trauma. Generally speaking, men show stronger psychopathic traits at the PCL-R and all psychopathic dimensions. A strong gender-oriented difference among several abuses and the development of psychopathy has not been highlighted yet. Sexual abuse has not been linked to higher levels of psychopathy, but it is the only type of abuse that shows higher frequency in primary psychopaths. This evidence is controversial because the severe adverse consequences of sexual abuse are well documented. It is feasible that sexual abuse might be less reported or disclosed, especially by men, due to stigmatization often linked to this type of abuse.

Although some kinds of abuse are associated with increased risk of developing psychopathy, with gender-oriented differences, the lack of biological explanations still limit knowledge on primary psychopathy.

CONCLUSION

Our work highlights a significant relation between trauma and psychopathy: EA, emotional neglect and physical abuse are the most frequent types of abuse related to psychopathy in males and females. Sexual abuse was the only kind of abuse that did not show a significant relation with psychopathy in most studies that we analyzed even if it was more frequent in women than men. A biological background, able to promote the onset of psychopathy is plausible and should be further investigated. Trauma is the key etiological factor of secondary psychopathy.

The most frequent limitations we detected were evaluations with self-reported scales since psychopaths have a high inclination to lie. Moreover, almost every study investigates inmates, a population with a more frequent history of trauma that could

biased the impact of trauma on psychopathy.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1177-1190

DOI: 10.5498/wjp.v11.i12.1177

ISSN 2220-3206 (online)

REVIEW

Polyamines and polyamine-metabolizing enzymes in schizophrenia: Current knowledge and concepts of therapy

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Author contributions: Bernstein HG designed the concept and wrote the paper; Keilhoff G contributed to the discussion and writing; Laube G contributed to the editing of the manuscript and review of the literature; Dobrowolny H designed Figure 1 and contributed to the discussion; Steiner J contributed to the writing and editing of the manuscript.

Conflict-of-interest statement: The authors report no conflict of interest.

Country/Territory of origin: Germany

Specialty type: Neurosciences

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0

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Abstract

Polyamines play preeminent roles in a variety of cellular functions in the central nervous system and other organs. A large body of evidence suggests that the polyamine pathway is prominently involved in the etiology and pathology of schizophrenia. Alterations in the expression and activity of polyamine metabolizing enzymes, as well as changes in the levels of the individual polyamines, their precursors and derivatives, have been measured in schizophrenia and animal models of the disease. Additionally, neuroleptic treatment has been shown to influence polyamine concentrations in brain and blood of individuals with schizophrenia. Thus, the polyamine system may appear to be a promising target for neuropharmacological treatment of schizophrenia. However, for a number of practical reasons there is currently only limited hope for a polyamine-based schizophrenia therapy.

Key Words: Polyamines; Spermidine; Spermine; Schizophrenia; Animal models; Therapy

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Core Tip: This review summarizes the advancements in research on the implications of polyamines and their metabolites for schizophrenia. Evidence from clinical and experimental studies show that some members of the polyamine regulatory system are altered in schizophrenia, but no polyamine-based therapy for schizophrenia is currently available.

Grade E (Poor): 0

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Received: February 4, 2021
Peer-review started: February 4, 2021
First decision: April 21, 2021
Revised: April 30, 2021
Accepted: November 18, 2021
Article in press: November 18, 2021
Published online: December 19, 2021

P-Reviewer: Guo WF
S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Gong ZM



Citation: Bernstein HG, Keilhoff G, Laube G, Dobrowolny H, Steiner J. Polyamines and polyamine-metabolizing enzymes in schizophrenia: Current knowledge and concepts of therapy. *World J Psychiatr* 2021; 11(12): 1177-1190
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1177.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1177

INTRODUCTION

Schizophrenia is one of the great scourges of humanity, affecting approximately 1% of the worldwide population. It is a devastating and debilitating mental illness, which appears to result from a complex interplay between genetic and environmental risk factors. Clinically, schizophrenia may be characterized by an array of positive, negative and cognitive symptoms, which include hallucinations, delusions, disorganized speech or executive function, impaired memory and reduced cognitive abilities[1]. Unfortunately, a large percentage of patients with schizophrenia suffer from treatment-resistance. Therefore, there is an urgent need for new treatment opportunity strategies.

Among putative therapeutic targets for schizophrenia treatment are polyamines (PAs), their precursors, derivatives and conversion enzymes. Aliphatic PAs constitute a small family of polycationic molecules derived from decarboxylation of ornithine[2], which play a crucial role in the developing and mature mammalian central nervous system (CNS). The initial suggestion that these were contributing factors to schizophrenia pathology dates back to the late 1950s, when it was shown that N,N-dimethyl-p-phenylenediamine oxidation rates were increased in sera of schizophrenia patients compared to non-psychotic individuals[3,4]. Since then, numerous papers have shown that the PAs, spermine, spermidine and putrescine, as well as their metabolites, are functionally linked with schizophrenia. The goal of this article is to review the current knowledge and insights about the role of the PA system in schizophrenia. Further, we attempt to assess the suitability of PA as targets for therapeutic intervention.

SEARCH STRATEGY

Using relevant search terms we searched published literature (including doctoral theses and patents) from 1 January 1955 to 21 January 2021 in PubMed and Google Scholar. Search terms were schizophrenia in combination with one or more of the following terms: polyamines, spermine, spermidine, putrescine, agmatine, S-adenosylmethionine, acrolein, L-ornithine decarboxylase, antizyme, antizyme inhibitor, spermine oxidase, spermidine synthase, spermidine/spermine N1-acetyltransferase, polyamine oxidase, S-adenosylmethionine decarboxylase, agmatinase and agmatinase-like protein. No language restrictions were applied.

THE PA PATHWAY IN THE HEALTHY CNS

Natural PAs, spermine and spermidine, and their precursor putrescine are present at relatively high concentrations in the mammalian brain. Because of the limited transport of PAs across the blood-brain barrier, their presence in the CNS should largely result from local synthesis (described previously in[5]). Brain PA content is tightly controlled through a complex network of biosynthetic and catabolic enzymes and a recently discovered transport system. However, while there are no doubts about the brain-borne origin of the largest fraction of cerebral PA, the precise cellular locus of PA biosynthesis has been a matter of contention for several years.

PAs are present at high concentrations both in glial cells (especially astroglia) and neurons[6-9]. Under normal conditions, neurons express L-ornithine decarboxylase (EC 4.1.1.17, ODC; Figure 1A), the rate-limiting enzyme of PA biosynthesis, which generates putrescine from ornithine[10,11]. This suggests that neurons are the primary source of newly synthesized PAs in the brain. Consequently, the observed strong astroglial immunostaining for spermidine and spermine would have to occur due to other reasons. Currently, it is certain that there is an efficient PA transport system involved in translocation of PAs from the site of synthesis in neurons to glial cells, a site of uptake, accumulation and release[9]. Indeed, various vesicular transporters for

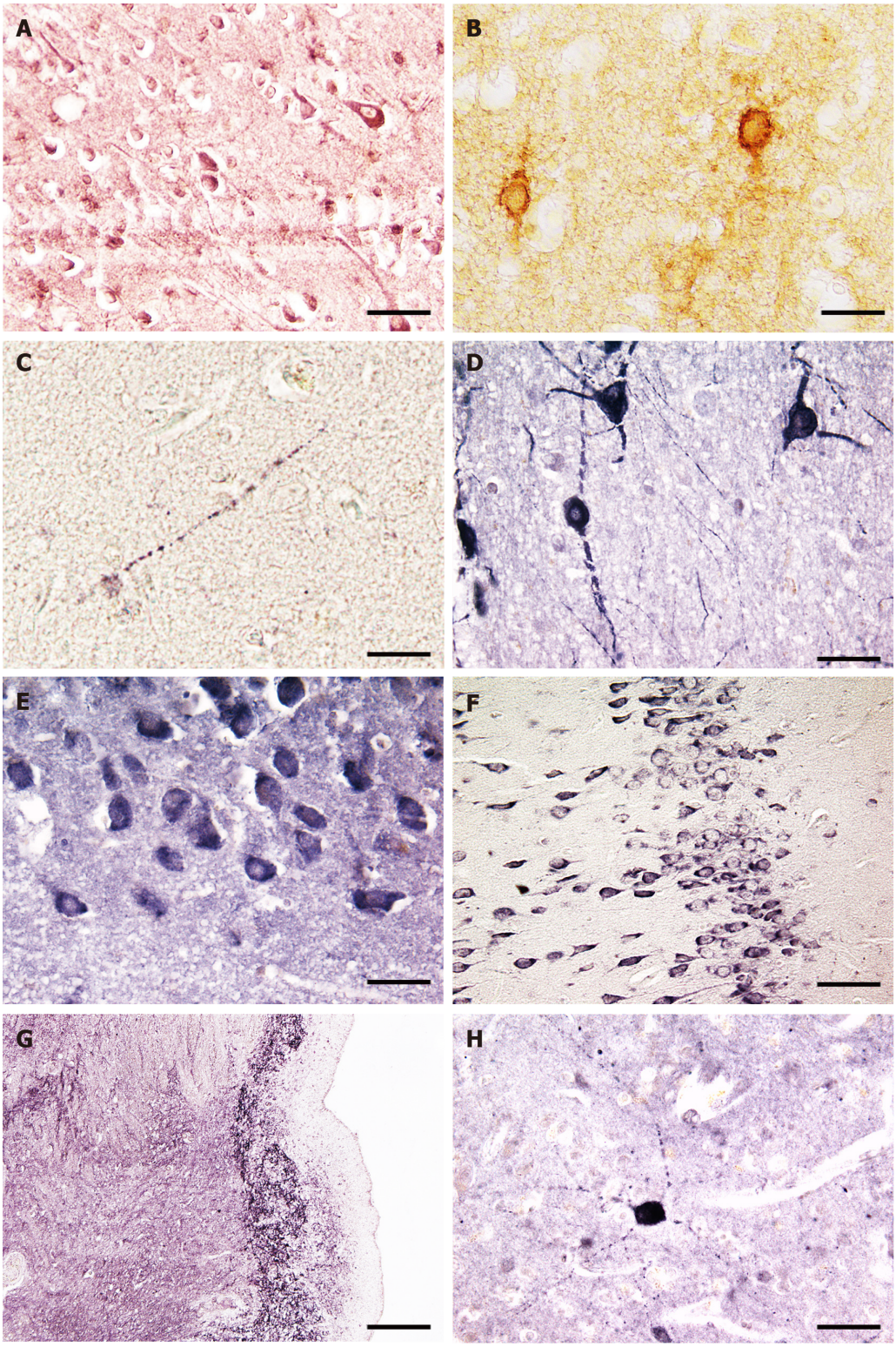


Figure 1 Cellular localization of polyamine-metabolizing enzymes and antizyme inhibitor 2 in human and rat brain with nickel-enhanced streptavidin-biotin immunocytochemistry. A: Ornithine decarboxylase immunoreactive neurons of the human prefrontal cortex. Bar = 70 μm; B: Antizyme inhibitor 2 expressing neurons in the human prefrontal cortex. Bar = 30 μm; C: Antizyme inhibitor 2 immunoreactive fiber in the human temporal cortex. Note the typical pearlchain-like structure as already described by others[18]. Bar = 20 μm; D: Strong spermine oxidase immunoreactive neurons in the human hypothalamus (interstitial nucleus). Bar = 30 μm; E: Multiple spermine oxidase expressing neurons in the CA2 region of the human hippocampus. Bar = 30 μm; F: Spermine oxidase expressing neurons in rat medial prefrontal cortex. Bar = 55 μm; G: Low power microphotograph of agmatinase immunoreactivity in human habenula. Bar = 140 μm; H: Single agmatinase immunopositive neuron in the human insular cortex. Bar = 30 μm.

PAs have been identified[12-15], and these may function bidirectionally[9].

Interestingly, other enzymes and enzyme regulators involved in the metabolism PAs are also predominantly or exclusively located in neurons. The ODC antizyme (which binds to ODC and thereby destabilizes and inactivates the enzyme) and

antizyme inhibitors 1 and 2 (AZINs, which both enhance ODC activity) have been found in neurons but not glia[16-18] (Figure 1B and C). Spermidine/spermine N1-acetyltransferase (EC 2.3.1.57, SAT1) is an enzyme responsible for PA interconversion. Its mRNA is widely distributed in neurons, with the highest concentrations found in the hippocampus and olfactory bulb[19]. The enzyme spermidine synthase (EC 2.5.1.22, which catalyzes the interconversion of S-adenosylmethionine to spermidine and 5'methylthioadenosine was localized to multiple rat brain neurons and neuropil of several brain regions [accumbens nucleus, hypothalamus, hippocampus (Figure 1E), cerebral cortex, striatum, cerebellum and others][20,21]. Spermine oxidase (EC 1.5.3.16, SMOX), which catalyzes the conversion of spermidine to spermine, is immunocytochemically detectable in many neurons of the cerebral cortex, hypothalamus, hippocampus, thalamus and cerebellum of human and rat brains (Figure 1D-F).

The neuromodulator agmatine, which is a precursor of putrescine, can be detected in synapses[22,23]. Agmatine is highly expressed in magnocellular hypothalamic neurons and many other nerve cell populations[23,24]. The agmatine-degrading enzyme, agmatinase (EC 3.5.3.11) was found in distinct interneurons of rat and human brain, located in cerebral cortex, hippocampus, habenula and cerebellum (Figure 1G and H)[25,26]. Interestingly, a second agmatine-metabolizing enzyme (called agmatinase-like protein) is present in rat brain neurons and astrocytes[27]. Finally, arginase (EC 3.5.3.1, ARG), which converts L-arginine into L-ornithine and urea, and arginine decarboxylase (EC 4.1.1.19, which catalyzes the conversion of L-arginine into agmatine and carbon dioxide) are widely expressed in rat brain neurons[28,29]. Thus, neurons harbor all PA synthesizing and degrading enzymes studied so far apart from the agmatinase-like protein, which is located mainly in astroglial cells[27]. However, the situation may be different in neonatal brains because recent evidence suggests that developing astroglial cells contain catalytically active ODC, synthesize PAs and release these[30]. The major reactions of the PA pathway are shown in Figure 2.

SOME CRITICAL FUNCTIONS OF PA IN THE CNS AT A GLANCE

The classical PAs, spermine, spermidine and putrescine are multifunctional chemical compounds, which serve a variety of important tasks in the CNS (for overviews see[5,9,10,30-32]). PA pathways play pivotal roles in the correct development of nervous tissue. There is experimental evidence to suggest that the replication of neurons and their precursor cells are dependent on the maintenance of certain region-and time-specific PA levels[32]. Depletion of PAs through inhibition of ODC arrests brain cell maturation, disrupts neuronal migration, disturbs the outgrowth of neurites and impairs the formation of synapses[11,31,32]. In addition, PAs are prominently involved in proliferation of neonatal astrocytes[30]. In both the pre- and postnatal CNS, PAs act as intracellular growth factors. By directly binding to DNA or the rough endoplasmic reticulum, spermine and spermidine increase the rate of cell growth and control protein synthesis of brain cells[11,33].

In the mammalian CNS PAs act as important endogenous modulators of glutamate receptors and are capable of altering the functioning of *N*-methyl-D-aspartate (NMDA) receptors. As NMDA receptor ligands, PAs exert both activator and inhibitor effects. On the one hand, PAs can enhance NMDA receptor currents by increasing the probability of channel opening. On the other hand, spermine is able to block NMDA channels in the open state, thereby reducing or blocking NMDA receptor currents by a voltage-dependent reduction of single-channel conductance[34,35]. Another inhibitory effect of spermine is to reduce the sensitivity to glutamate (or other glutamate site agonists) at NMDA receptors composed of NMDA receptor 1/NMDA receptor 2B subunits by reducing the affinity for glutamate[34]. PAs also contribute to alterations of membrane excitability by interacting with ionotropic kainate and AMPA glutamate receptors (discussed in detail in[36]). Modulation of glutamate signaling by PA influences a variety of functional processes in the brain, ranging from regulation of neuronal and glial excitability to memory and aging[37].

Another mechanism through which PAs exert influence on membrane excitability is the blockade of outward potassium currents through, consequently so-called, inwardly-rectifying potassium channels. Inwardly-rectifying potassium channels exhibit a sharp voltage dependence and crucially contribute to maintenance of the resting membrane potential. Thus, they are involved in the regulation of bioelectrical excitation of many cell types including neurons and glial cells[9,37-40]. The basic mechanism underlying this steep voltage dependence is the channel blockade by PA and magnesium. PAs are thought to enter the inwardly-rectifying potassium channel

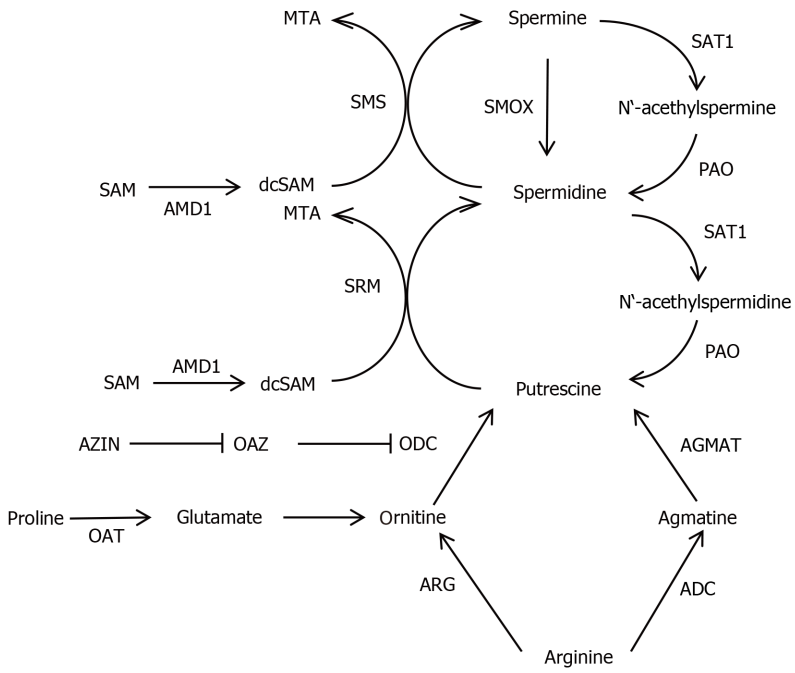


Figure 2 Major pathways of polyamines biosynthesis and interconversion (from Gross and Turecki[71]; scheme reproduced with permission of Bentham; modified). ADC: Arginine decarboxylase; AGMAT: Agmatinase; AMD: S-adenosylmethionine decarboxylase; ARG: Arginase; AZIN: Ornithine decarboxylase antizyme inhibitor; dcSAM: Decarboxylated S-adenosylmethionine; MTA: 5'-methylthioadenosine; OAT: Ornithine aminotransferase; OAZ: Ornithine decarboxylase antizyme; ODC: Ornithine decarboxylase; PAO: Polyamine oxidase; SAM: S-adenosylmethionine; SAT1: Spermidine/SpermineN1 acetyltransferase; SMS: Spermine synthase; SMOX: Spermine oxidase; SRM: Spermidine synthase.

pore *via* the intracellular side of the membrane and displace multiple ions during their stable binding site within the channel[40].

Lastly, PAs act as free radical scavengers and effective antioxidants. This role is unrelated to the activation of the NMDA receptor[41]. Of note, PA catabolism, which is upregulated after traumatic brain injury and other stressful situations, can be a source of toxic reactive oxygen species[41,42].

The PA agmatine, a decarboxylation product of arginine, is an endogenous ligand of imidazoline, α_2-adrenergic and glutamatergic NMDA receptors[43,44]. Agmatine is a neuromodulator and neurotransmitter, which significantly contributes to the regulation of various neurotransmitters and signaling pathways (reviewed in[43-47]). Several studies have demonstrated that agmatine is involved in cognitive processes [47-50]. In addition, it performs a neuroprotective function by reducing oxidative damage, neuroinflammation and proapoptotic signaling[43,51].

THE PA SYSTEM IN SCHIZOPHRENIA

In the early 1980s it was hypothesized that PA might play a central role in the etiology of schizophrenia[52]. Since then, numerous papers have appeared in support of this conjecture, while others call in question a significant role of PA in schizophrenia development and persistence.

GENETIC ASPECTS OF PA METABOLISM IN SCHIZOPHRENIA

Compared with psychically healthy individuals, tissue and body fluid concentrations of some PAs are altered in patients suffering from schizophrenia. Since single nucleotide polymorphisms in the intron region of *ODC* (+316 G>A) and the promoter region of the SAT1 encoding gene *SAT* (1415 T>C) genes are known to be associated with the expression levels of PAs[53], both gene polymorphisms might be potential genetic markers for susceptibility to schizophrenia. Only the *SAT 1* gene polymorphism has been studied so far. There were no significant differences in the distribution of the genotypes of the *SAT*-1415 T/C single nucleotide polymorphisms

between schizophrenia patients, non-psychotic psychiatric patients and healthy controls. However, a "mild association" between the C allele and psychopathology was found for the female group[54]. A translational convergent functional genomics study identified *AZIN 1*, the gene encoding antizyme inhibitor 1, as a candidate gene for schizophrenia (convergent functional genomics score 3.0[55]).

ALTERATIONS IN GENE EXPRESSION, ENZYME ACTIVITIES AND EPIGENETIC REGULATION OF PA-RELATED GENES IN SCHIZOPHRENIA

A comprehensive DNA microarray study revealed that the expression of *AZIN 1* was reduced in almost all samples from subjects with schizophrenia. In addition, reduced cellular expression of AZIN 1 was verified by *in situ* hybridization of postmortem brain samples of the same schizophrenia subjects. Of note, this reduction was not a consequence of long-term neuroleptic treatment of the patients since there was only a marginal reduction of AZIN 1 expression in haloperidol treated monkeys[56]. Ornithine aminotransferase (EC 2.6.1.13) is an enzyme that has been indirectly connected with PA metabolism through catalyzing the formation of glutamate or proline from ornithine[57]. This enzyme was found to be reduced in samples from schizophrenia patients[56]. However, other studies were unable to replicate these findings. Maycox *et al*[58] could not identify any differentially expressed genes implicated in PA metabolism in two large schizophrenia cohorts (with more than 30000 mRNA transcripts).

Numerous communications have dealt with altered expression and/or activity of PA-metabolizing enzymes in brain tissue or blood of schizophrenia patients. Conflicting findings exist regarding polyamine oxidase(PAO). Blood plasma PAO activity was reportedly lower in acute schizophrenia patients[59,60]. This decrease in activity was unrelated to the subtype of schizophrenia (paranoid *vs* non-paranoid), age of onset or neuroleptic treatment[60-62]. In contrast with these findings, Dahel *et al*[63] and Das *et al*[64] found increased PAO activity in blood sera from schizophrenic patients, which was reduced by electroconvulsive therapy[63]. On the other hand, ODC activity was found to be normal in prefrontal cortex and hippocampus autopsy samples from people who suffered from schizophrenia[65], and there were no differences with regard to the number of ODC immunoreactive entorhinal cortex neurons between schizophrenia patients and controls[5]. Another study that measured SMOX activity found increased activity in sera from schizophrenia patients compared to non-psychotic controls[66], whereas AMD and SAT1 activities were unaltered in prefrontal cortex and hippocampus tissue of schizophrenia patients[65].

The density of agmatinase-containing interneurons was lower in the hippocampus of schizophrenia patients in comparison with controls[43]. Significantly increased activity of ARG (a gate keeper enzyme of PA synthesis) was observed in the cerebrospinal fluid of schizophrenia patients[67]. Lastly, increased enzyme activity and ARG II protein expression were found in postmortem brain tissue specimen in schizophrenia[68], whereas plasma ARG activity was significantly lower in schizophrenia than in controls[69].

There is evidence that gene regulation *via* epigenetic modifications play a major role in schizophrenia pathophysiology. However, in contrast to other mental disorders and suicide, no such modifications for PA metabolizing genes in schizophrenia have been identified[70-72].

PA CONTENT IN TISSUES AND BODY FLUIDS IN SCHIZOPHRENIA

Several reports have targeted the levels of cerebral and peripheral PA in schizophrenia patients. Elevated blood concentrations of spermine and/or spermidine have been measured in treated schizophrenia patients[73,74] and in drug-naïve cases[75], whereby long-term neuroleptic treatment was shown to reduce spermine levels[75,76]. Also, increased concentrations of spermidine and total PA were detected in fibroblasts obtained from schizophrenia patients (reviewed in[11]). So far, little information is available regarding brain PA concentrations in schizophrenia. Gilad *et al*[65] could not find significant alterations of PA levels in postmortem brain tissue of schizophrenia persons compared with controls. However, a more recent paper described significantly elevated levels of spermine, spermidine and putrescine in many brain regions of psychotic individuals[77].

Significantly increased agmatine concentrations were measured in blood plasma and postmortem frontal cortex tissue of individuals with first episode and chronic schizophrenia[68,78-80], and antipsychotic treatment was found to decrease blood agmatine levels[77]. In contrast to the previously mentioned work, reduced blood agmatine levels were measured in early-onset schizophrenia[81]. The amino acid L-arginine is metabolized by ARG, which is the first step in PA synthesis. Increased blood plasma arginine levels were reported in medication-naïve, first episode patients. Medication had no influence on enhanced blood concentrations in schizophrenia patients[79]. Finally, two-fold increased concentrations of S-adenosylmethionine were found in prefrontal cortex samples of schizophrenia patients compared with controls. This drastically increased brain S-adenosylmethionine content was not affected by postmortem interval or medication[82]. The main findings regarding this are summarized in Table 1.

PA IN THE CNS OF SUICIDE COMPLETERS

Numerous studies have shown alterations of PA and PA-metabolizing enzymes in individuals who died by suicide (reviewed in[5,71,83]). However, a closer look at these studies reveals that they all provide findings from individuals who had suffered from major depression or from suicide victims with no specified psychiatric diagnosis but not from those with schizophrenia. Thus, it would be interesting to determine if schizophrenia patients who died by suicide would differ from non-suicide schizophrenia persons with regards to PA levels.

PA IN ANIMAL MODELS OF SCHIZOPHRENIA

A promising approach to identify and better understand diverse schizophrenia symptoms in humans has been to investigate behavioral phenotypes in animal models of the disease[84]. Although numerous animal models of schizophrenia have been introduced so far, only a few of these have accounted for the role of PAs and their metabolites. We studied the cellular expression of ODC in rats with neonatal lesions of the ventral hippocampus and found increased immunostaining in the prefrontal, perirhinal and entorhinal cortex[85]. In addition, we found an increased density of SMOX-immunoreactive medial prefrontal neurons (unpublished findings). Increased levels of putrescine, spermidine, spermine and arginine and decreased levels of agmatine were found in the prefrontal cortex and hippocampus of male and female rat offspring after maternal immune activation[86].

Prepulse inhibition of the startle reflex response is disturbed in schizophrenia, although there are conflicting findings regarding the influence of agmatine on this effect. In one study, agmatine was reported to disrupt prepulse inhibition in rats[87], whereas another investigation found that low doses of agmatine attenuated the disruptive effects of the psychotomimetic substance phencyclidine on this response [88]. Other studies showed that agmatine depressed conditioned avoidance response and enhanced the inhibitory effect of haloperidol and olanzapine on this readout. Furthermore, agmatine attenuated apomorphine induced climbing and diminished amphetamine or ketamine induced hyperlocomotor activity[89,90]. Injection of phencyclidine, which induces psychotic symptoms in healthy individuals, was shown to also alter arginine metabolism in the rat hippocampus and prefrontal cortex[90], and withdrawal from repeated phencyclidine administration has been found to alter ARG activity as well as the concentration of arginine metabolites in rat brain[68].

Interestingly, transgenic animals, which overexpress ODC and/or SAT1, show a variety of neuroanatomical, neurochemical and behavioral peculiarities but not schizophrenia-like behavior[91]. SMOX overexpression in the neocortex in Dach-SMOX mice leads to glutamate excitotoxicity[92], which is a characteristic feature of human schizophrenia[93-95]. The main findings regarding this are summarized in Table 2.

POSSIBLE IMPACT OF PA PATHWAY ABNORMALITIES ON SCHIZOPHRENIA PATHOLOGY

PAs and their metabolites are crucial factors in a variety of functions, which are disrupted in schizophrenia. These disease-related functional impairments range from

Table 1 Summary of polyamine-related findings in human schizophrenia studies

No significant differences in the distribution of the genotypes of the *SAT*-1415 T/C SNP between schizophrenia patients and healthy controls[54].
CFG study identified *AZIN 1* as a candidate gene for schizophrenia[55].
DNA microarray and *in situ* hybridization studies show decreased AZIN 1 expression in schizophrenia. No influence of neuroleptic treatment[56].
OAT expression is reduced in samples of schizophrenia individuals[56,57].
No differently expressed genes implicated in PA metabolism in two large schizophrenia cohorts[58].
PAO activity is lower in blood plasma of acute and chronic schizophrenia patients[59-62].
PAO activity increased in blood sera of schizophrenic patients[64,65], reduction by electroconvulsive therapy[62].
ODC activity and cellular expression is normal in brain autopsy samples from people who suffered from schizophrenia[65,66].
SMOX activity is markedly higher in sera of schizophrenic patients[67].
AMDI and SAT1 activities are unaltered in brain tissue of schizophrenia individuals[65].
Density of AGMAT-containing interneurons is reduced in the hippocampus of schizophrenia patients[43].
Increased ARG activity in the CSF of schizophrenia patients[67].
Increased ARGII activity and protein expression in postmortem brain tissue in schizophrenia[68].
ARG activity is lower in plasma of schizophrenia individuals[71].
Elevated blood concentrations of spermine and/or spermidine in drug-naïve and treated schizophrenia patients[73-75].
Long-term neuroleptic treatment reduces spermine levels[76,77].
Increased concentrations of spermidine and total PA in fibroblasts from schizophrenia patients (reviewed in[11]).
PA levels normal in postmortem brain tissue of schizophrenia persons[65].
Elevated levels of spermine, spermidine and putrescine in brains of psychotic individuals[77].
Increased agmatine concentrations in blood plasma and postmortem brains of individuals with first episode and chronic schizophrenia[68,78-80].
Antipsychotic treatment decreases blood agmatine levels[77].
Reduced blood agmatine concentrations in early-onset schizophrenia[81].
Increased concentrations of SAM in brain samples of schizophrenia patients[82].

SNP: Singlenucleotide polymorphism; OAT: Ornithine aminotransferase; ODC: Ornithine decarboxylase; SMOX: Spermine oxidase; AGMAT: Agmatinase; AMD: S-adenosylmethionine decarboxylase; ARG: Arginase; PA: Polyamines; CSF: Cerebrospinal fluid; CFG: Convergent functional genomics; SAM: S-adenosylmethionine; SAT1: Spermidine/Spermine N1 acetyltransferase; PAO: Polyamine oxidase; AZIN: Antizyme inhibitor.

abnormal prenatal CNS development (disrupted neuronal migration and other pathological processes), impaired glutamate receptor functioning, glia pathology and immune dysregulation, to serious cognition problems and bizarre behavior. Thus, it is conceivable that altered PA supply and/or action contribute to the initiation and further progression of these impairments. More specifically, since spermine and spermidine positively influence many of these disturbed cellular mechanisms (see our considerations about PA functions), one may expect deficits in brain PA content in schizophrenia. Curiously, the opposite is the case as either increased blood and brain levels[73-75] or normal concentrations[65] of PA and ODC[81,85,87] have been reported for schizophrenia and animal disease models. Moreover, increased PA levels are not the result of neuroleptic treatment since anti-psychotics decrease PA concentrations in tissues and blood[75,76]. Thus, it seems unlikely that increased concentrations of spermine or other PAs contribute to schizophrenia pathology. In particular, there is no evidence that a PA excess is involved in impaired NMDA receptor functioning as observed in schizophrenia[34].

The situation is less evident with agmatine, which shows beneficial effects on some of the functions disrupted in schizophrenia. Increased agmatine concentrations were determined in blood plasma and post-mortem brain of individuals with first episode and chronic schizophrenia[68,76-81]. In contrast, reduced levels were measured in brain tissue of rat offspring after maternal immune activation[86]. It cannot be excluded, however, that overproduction of PA in human schizophrenia represents an attempt to compensate for certain functional losses (for example, induction and promotion of autophagy[95-97], which is abnormally reduced in schizophrenia[96]).

Table 2 Summary of polyamine-related findings in studies of animal models

Neuronal expression of ODC increased in rats with neonatal lesion of the ventral hippocampus[85].
Neuronal expression of SMOX increased in rats with neonatal lesion of the ventral hippocampus (unpublished).
Increased brain levels of putrescine, spermidine, spermine and arginine but decreased levels of agmatine were measured in rat offspring after maternal immune activation[86].
Agmatine disrupts prepulse inhibition in rats[87].
Agmatine attenuates the disruptive effects of phencyclidine on prepulse inhibition[88,89].
Injection of phencyclidine alters arginine metabolism in rat brain[90].
Withdrawal from repeated phencyclidine administration alters ARG activity and the levels of arginine metabolites in rat brain tissue[91,92].
No schizophrenia-like behavior in transgenic animals that overexpress ODC and/or SAT1[91].
SMOX overexpression in mice leads to glutamate excitotoxicity[91,92], a characteristic feature of "human" schizophrenia.

ARG: Arginase; ODC: Ornithine decarboxylase; SAT1: Spermidine/SpermineN1 acetyltransferase; SMOX: Spermine oxidase.

In addition, the possibility cannot be excluded that there may be a PA deficit in the developing CNS of future schizophrenia patients, which would contribute to disturbed prenatal brain development[11,96]. However, the latter scenario is not likely since increased concentrations of PA have been determined in rat offspring after maternal immune activation, a suitable neurodevelopmental model of the disease[86].

While the findings showing that increased PA and agmatine levels would not serve as convincing arguments in support of their involvement in schizophrenia pathology, it is possible that increased expression and enzyme activity of SMOX is a contributing factor[66]. SMOX catalyzes the oxidation of spermine to produce spermidine, hydrogen peroxide (H_2O_2) and 3-aminopropanal, which may spontaneously be converted to acrolein[97]. Consequently, increased oxidative stress was identified in SMOX over-expressing Dach-SMOX mice[92] which resulted in glu, tamate excitotoxicity[92,95]. Both reactive oxygen species, hydrogen peroxide and acrolein, are highly cytotoxic, as these can lead to production of massive cellular damage and pathologies[98-101]. Interestingly, in major depression and schizophrenia patients, significantly increased concentrations of protein-conjugated acrolein were measured, which could be reduced by anti-psychotic medication[101]. There is ample evidence that oxidative stress is a core feature in schizophrenia (for recent comprehensive reviews, see[101-104]). Oxidative stress is thought to be one of the mediators of progressive changes in brain structure and function in schizophrenia, which take place as schizophrenia progresses. The pathophysiological consequences include gray matter loss, myelination deficits and subsequent cognitive and functional impairment [105].

The extent that increased SMOX activity contributes to the aberrantly activated immune[104] and inflammatory[106] processes in schizophrenia remains to be established.

THE PA PATHWAY – A TARGET FOR NEW THERAPIES?

In schizophrenia, the brain and blood levels of PAs are normal or even increased. Hence, higher dietary intake of spermine or spermidine[43,107] cannot be a suitable approach to remove or mitigate schizophrenia symptoms. A potentially more promising approach would be to reduce SMOX expression or activity in order to diminish the generation of hydrogen peroxide and acrolein. Indeed, it has been shown recently that targeting SMOX is neuroprotective in a model of ischemic brain damage [108]. In this context, however, two questions need to be answered: (1) How to depress SMOX activity; and (2) What would be the consequences of this? In general, there are only a few approaches for a potentially successful intervention in this pathway. One of these is the application of the SMOX inhibitor *N*-(3-{[3-(dimethylamino)propyl] amino}propyl)-8-quinolinecarboxamide, which is under consideration for anti-cancer therapy[107]. Another one is the irreversible inhibition of SMOX by use of the PAO inhibitor MDL72527 {N1,N4-(bis(2,3-butadienyl)-1,4-butanediamine)}[108]. However, the application of both enzyme inhibitors produces a number of serious side effects. Furthermore, SMOX has an essential role in normal brain PA homeostasis (for review,

see[101,107,108]), which might be disrupted by any kind of intervention. Thus, the use of these enzyme inhibitors for schizophrenia therapy does not appear to be viable. Hence, PA-based schizophrenia therapy will probably remain an unresolved issue in the foreseeable future.

CONCLUSION

The PA system plays an essential role in the brain and other organs. Over the past half century, numerous reports appeared that showed that PAs, their precursors and derivatives, as well as some PA-metabolizing enzymes, are altered in schizophrenia, thus giving rise to the possibility for new PA-based therapies. Unfortunately, there are currently no prospects for such a therapeutic intervention, given a number of currently insurmountable obstacles. Therefore, further studies are urgently needed to learn more about the relationship between the PA system and schizophrenia pathology.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1191-1205

DOI: 10.5498/wjp.v11.i12.1191

ISSN 2220-3206 (online)

REVIEW

Nuclear receptors modulate inflammasomes in the pathophysiology and treatment of major depressive disorder

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Author contributions: Wang H wrote the first draft of the manuscript; Kan WJ, Feng Y, Feng L, Yang Y, Chen P, and Xu JJ managed the systematic literature search; Du J supervised the study; Si TM, Zhang L, and Wang G critically revised the manuscript; and all authors approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest for this manuscript.

Supported by the National Natural Science Foundation of China, No. 31650005.

Country/Territory of origin: China

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

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Abstract

Major depressive disorder (MDD) is highly prevalent and is a significant cause of mortality and morbidity worldwide. Currently, conventional pharmacological treatments for MDD produce temporary remission in < 50% of patients; therefore, there is an urgent need for a wider spectrum of novel antidepressants to target newly discovered underlying disease mechanisms. Accumulated evidence has shown that immune inflammation, particularly inflammasome activity, plays an important role in the pathophysiology of MDD. In this review, we summarize the evidence on nuclear receptors (NRs), such as glucocorticoid receptor, mineralocorticoid receptor, estrogen receptor, aryl hydrocarbon receptor, and peroxisome proliferator-activated receptor, in modulating the inflammasome activity and depression-associated behaviors. This review provides evidence from an endocrine perspective to understand the role of activated NRs in the pathophysiology of MDD, and to provide insight for the discovery of antidepressants with novel mechanisms for this devastating disorder.

Key Words: Major depressive disorder; Immune inflammation; Inflammasome; Nuclear receptors

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Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: March 1, 2021
Peer-review started: March 1, 2021
First decision: July 15, 2021
Revised: July 29, 2021
Accepted: November 2, 2021
Article in press: November 2, 2021
Published online: December 19, 2021

P-Reviewer: Kotzalidis GD
S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Wang JJ

Core Tip: We summarize the evidence on nuclear receptors (NRs), such as glucocorticoid receptor, mineralocorticoid receptor, estrogen receptor, aryl hydrocarbon receptor, and peroxisome proliferator-activated receptor, in modulating inflammasome activity and depression-associated behaviors. This review provides evidence from an endocrine perspective to understand the role of activated NRs in the pathophysiology and treatment of major depressive disorder. Hopefully, the modulation of NRs with hormones and metabolites may become one of the key endocrinologic mechanisms for the development of novel therapeutics to increase the likelihood of therapeutic efficacy.

Citation: Wang H, Kan WJ, Feng Y, Feng L, Yang Y, Chen P, Xu JJ, Si TM, Zhang L, Wang G, Du J. Nuclear receptors modulate inflammasomes in the pathophysiology and treatment of major depressive disorder. *World J Psychiatr* 2021; 11(12): 1191-1205
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1191.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1191

INTRODUCTION

Major depressive disorder (MDD) is common, has a high recurrence rate and disability rate, and affects approximately 300 million people worldwide[1]. However, the underlying pathophysiological mechanisms of MDD have yet to be completely understood. Although effective treatments are available, market-approved antidepressants have many problems, such as a single mechanism of action, delayed effect [2], and numerous side effects[3], and approximately one third of all patients fail to respond to conventional antidepressants[4]. Accordingly, there is an urgent need for new conceptual frameworks and perspectives to understand the occurrence and development of depression to develop better treatments. As another important hypothesis of depression, several lines of evidence have established an association between MDD and the neuroimmune pathway, although some psychiatrists have argued about the causal relationship between inflammation and depression[5-7]. In this review, we outline emerging data that point to nuclear receptors (NRs) as potentially important contributors to the pathophysiology of depression. We first review the current research on the inflammatory hypothesis of depression, and investigate the role of inflammasomes in the neuroimmune pathway of depression. The regulatory roles of NRs [including glucocorticoid receptor (GR), mineralocorticoid receptor (MR), estrogen receptor (ER), aryl hydrocarbon receptor (AHR), and peroxisome proliferator-activated receptor (PPAR)] in inflammasome activation and pathophysiology of depression are also investigated. Finally, these interactions are discussed as a foundation for new therapeutics that target the NRs to treat depression.

INFLAMMATION AND MDD

Inflammatory response is a survival mechanism in human self-protection, which is the defensive response of the body to various traumatic stimuli. Endogenous or exogenous pathogens and tissue damage are initially detected by pattern recognition receptors (PRRs), such as Toll-like receptors and nucleotide-binding oligomerization domain (NOD)-like receptors, mainly expressed by cells that participate in the innate immune response[8]. Following the activation of such receptors, signals are then transmitted to activate transcription factors. These factors regulate hundreds of genes that increase the initial inflammatory response. The brain has its own highly complex immune regulation system and is closely connected with the peripheral immune system[9]. Crosstalk between the immune system and the central nervous system (CNS) is very important for the establishment of appropriate immunity against infection and injury, the maintenance of mental health, and the influence of behavioral response[10].

The role of inflammation in the causation and exacerbation of MDD is supported by the findings from clinical studies that patients with chronic inflammation (*e.g.*, asthma [11,12] and meningitis[13,14]), tumors, and autoimmune diseases (*e.g.*, multiple

sclerosis[15,16], Guillain-Barre syndrome[17], and systemic lupus erythematosus[18,19]) are more likely to suffer from depression, the secretion of inflammation-activated cytokines [interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNFα), and C-reactive protein] in the peripheral blood and cerebrospinal fluid of patients with depression is increased[20,21], microglial activation and neuro-inflammation were found in the brain of patients with depression examined post mortem[22], and both nonsteroidal anti-inflammatory drugs and cytokine inhibitors have an active therapeutic effect on depression[23-25]. Preclinical studies have demonstrated that repeated stress events cause neurobiological changes including synaptic plasticity deficits[26] and neurotransmitter system dysregulation[27,28], leading to depressive-like behavior. Apart from these neurobiological responses, exposure to stress also has physiological and immunological consequences such as increased expression of inflammatory cytokines (such as IL-1β, TNFα, and IL-6) in the blood and brain[29]. Although cumulative evidence supports that immune inflammation plays a very important role in the pathogenesis of depression, the exact mechanism remains unclear.

INFLAMMASOMES IN THE NEUROIMMUNE PATHWAY OF MDD

The term 'inflammasome' was first proposed by the Tschopp research group in 2002 [30]. Inflammasomes are multiprotein complexes (-700 KD) composed of intracellular PRRs, and are an important part of the innate immune system. They can recognize pathogen-associated molecular patterns (PAMPs, such as lipopolysaccharide and bacteria) or host-derived danger signaling molecular patterns [DAMPs, including adenosine triphosphate (ATP), heat shock proteins (Hsp), glucose, uric acid, high mobility group box 1, and molecules associated with oxidative stress], and can recruit and activate pro-caspase-1. Activated caspase-1 cleaves the precursors of IL-1β and IL-18 to produce corresponding mature cytokines[31]. Activated inflammasomes can also induce apoptosis. Over the past 18 years, extensive research in this area has illustrated the key components of inflammasome activation and its role in disease processes. To date, five receptor proteins have been found to assemble inflammasomes, consisting of the NOD, leucine rich repeat (LRR)-containing protein (NLR) family members NLRP1, NLRP3, and NLRC4, as well as the proteins absent in melanoma 2 and pyrin[32]. The existing evidence suggests that NLRP1 and NLRP3 inflammasomes, especially NLRP3, play an important role in the neuroimmune pathway of MDD[33].

NLRP1 inflammasome

NLRP1 is the first identified inflammasome sensor protein[31]. Humans only have one NLRP1 protein, containing PYD, NOD, and LRRs domains, a function-to-find domain, and a carboxy-terminal caspase-associated recruitment domain[31]. The NLRP1 inflammasome, mainly expressed in neurons, is predominantly implicated in pathologies of neuronal injury and cognitive impairment, which are core features of MDD[34,35]. Although no clinical studies have reported the NLRP1 inflammasome changes in the pathogenesis of MDD patients, animal studies suggest that the NLRP1 inflammasome may play an important regulatory role in depressive-like behavior. Li *et al*[36] found that inhibiting the product of NLRP1 inflammasome could eliminate the depression-like behaviors caused by a chronic constriction injury. Recent studies showed that chronic unpredictable mild stress (CUMS) increased the expression of NLRP1 inflammasome complexes and pro-inflammatory cytokines. Hippocampal *Nlrp1a* knockdown prevented the NLRP1 inflammasome-driven inflammatory response and improved CUMS-induced depressive-like behaviors[37]. The above results suggest that NLRP1 inflammasome may be a potential antidepressant target, and further mechanisms need to be clarified.

NLRP3 inflammasome

Unlike NLRP1, NLRP3, mostly expressed in microglia cells, is activated by the most diverse array of danger signals[33,34]. NLRP3 has been reported to participate in the pathophysiology of depression in animal models and MDD patients. Supporting the hidden role of the NLRP3 inflammasome in MDD patients are data demonstrating that NLRP3 activation is increased in peripheral blood mononuclear cells[38,39]. Preclinical evidence linking the NLRP3 inflammasome to depressive-like behaviors has been found in numerous animal models, including an acute model of systemic lipopolysaccharide administration[40], chronic stress models[33], and ovariectomy and estrogen-deficient mice. These models can lead to depressive-like behavior and up-regulation of NLRP3 expression in rodents. Down-regulation of the expression of NLRP3 by some

biological methods can reverse depression-like behavior[41]. NLRP3 inflammasome-driven pathways in depression have been widely reviewed[42]. In brief, psychological stress and danger substances can activate the NLRP3 inflammasome, which may lead to the release of pro-inflammatory cytokines and induction of depression. Next, we will focus on the role of NRs in the activation of inflammatory bodies in the following chapters.

ROLE OF NRS IN REGULATION OF INFLAMMASOMES AND DEPRESSION

The NR superfamily is a family of ligand-regulated transcription factors that are widely expressed throughout the body[43]. NRs are activated by steroid hormones, such as androgen, estrogen, and progesterone, and other lipid-soluble signals, including oxysterols, retinoic acid, and thyroid hormone, and regulate the expression of a wide range of genes linked to metabolism and inflammation. There are 49 known members in humans[43]. All NR superfamily members have a common architecture, containing a variable N-terminal domain, a central DNA binding domain (DBD), a hinge region, a carboxy-terminal ligand-binding domain (LBD), and a variable C-terminal domain[44]. Of these, the DBD and LBD are the two most highly conservative binding domains. The DBD contains two zinc-fingers, which act as a hook, that provide base-specific binding to sequences in the vicinity of target genes. The LBD of NRs consists of a three-layered, antiparallel, helical sandwich and is connected to the DBD by a flexible hinge domain. According to the key characteristics of dimerization, DNA binding motifs, and ligand binding, NRs can be broadly divided into four classes [steroid receptors, retinoid X receptor (RXR) heterodimers, homodimeric orphan receptors, and monomeric orphan receptors][45]. There are some obvious structural and functional differences between different classes, and the role of different NRs in the neuroimmune mechanism of MDD are described.

NRs in MDD

GR

GR is a member of the steroid receptors, and is activated by the endogenous steroid hormone cortisol[46]. Unliganded GR is predominantly localized within the cytoplasm [47]. Glucocorticoid (GC) binding causes conformational changes of the GR and activates multiple functional domains, including the hinge and LBD regions. After rapidly and efficiently being transported to the nucleus, the GR binds to the specific GC response elements of the genome to form a nuclear complex containing the GR and co-regulatory factors, which jointly activate or inhibit the transcription of GC responsive genes[48].

The participation of GR down-regulation in the pathophysiology of MDD has been demonstrated in clinical and preclinical studies. Drug-free MDD patients have reduced *GR* mRNA expression together with increased expression of the FK506 binding protein 5[49,50], which reduces GR function and promotes inflammation by coordinating with Hsp90. Kang *et al*[51] found an association between the methylation of GRs and depression later in life. A meta-analysis demonstrated that the *NR3C1* (GR) rs41423247 homozygous mutation may be a risk factor for MDD [odds ratio (OR): 0.77, 95% cumulative incidence (CI): 0.64-0.94, $P = 0.01$][52]. Studies on transgenic mice and a mouse stress model found that the down-regulation of GR expression is significantly related to depressive-like behavior[53]. Exogenous GC exacerbates depressive-like behavior, and down-regulates GR expression. In addition, accumulating evidence has illustrated that GR antagonists, such as mifepristone, ameliorate psychotic symptoms and cognitive deficits in MDD and bipolar disorder[54,55]. However, this seems to contradict the hypothesis of enhanced immune inflammatory response in MDD, as GC is one of the most effective anti-inflammatory hormones in the body.

It is also understandable that the effect of GR on the immune system and synapse is highly dependent on the time and dose. Mounting data indicate that innate immune cytokines cause insufficient GC signals by decreasing GR expression, blocking translocation of the GR from the cytoplasm to the nucleus, and disrupting GR-DNA binding through nuclear protein-protein interactions, which may be a reasonable explanation for this problem. Escoter-Torres *et al*[56] have reviewed the mechanisms of inflammatory gene regulation by the GR. Here, we will mainly explore the relationship between GR and inflammasomes in the pathophysiological mechanism of MDD.

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction was assumed to be due to aberrant adrenal GC secretion and disorderly hormone feedback loops in MDD patients[57]. GC-induced activation of the NLRP3 inflammasome may mediate the potentiated neuroinflammation[58]. However, whether the effects of inflammasome activation and the HPA axis are regulated through GR-related pathways is still unclear. Nevertheless, some evidence suggests that the GR is closely related to inflammasomes, which play an important regulatory role in some immune inflammatory diseases, such as MDD and acute-on-chronic hepatitis B liver failure[59]. In chronic obstructive pulmonary disease-induced depression, GR dysfunction mediates activation of the NLRP3 inflammasome. Preclinical evidence has shown that activation of the GR-NF-κB-NLRP3 pathway in microglia mediated chronic stress-induced neuroinflammation and depressive-like behavior[60]. Chronic corticosterone (CORT) treatment can increase Txnip and upregulate Txnip-NLRP3 binding, which activated the NLRP3 inflammasome, and induced the activation of caspase-1 and the release of IL-1β[61]. In addition, chronic GC exposure may increase neuroinflammation through NLRP1 inflammasome activation and induce neurodegeneration[62]. In conclusion, subsequent studies should be devoted to exploring how GR regulates the activation of inflammatory bodies and thus regulates the neuroimmune response.

MR

Negative feedback regulation of the HPA axis requires the participation of the dual-receptor system of MR and GR[63]. Similar to GR, MR is another member of steroid receptor and ligand-inducible transcription factors. In the brain, MR has approximately 10-fold higher affinity for CORT than the GR[64]. Due to the differences in affinity, CORT at the basal level largely occupies the MR, whereas higher hormone levels progressively occupy the GR after stress and circadian/ultradian peaks[65]. Early research results showed that brain MRs did not play an important role in the regulation of the stress response; however, subsequent studies demonstrated that MRs were essential for nongenomic regulation of glutamate transmission in the hippocampus by CORT. Based on this, considering that MRs are expressed abundantly in the limbic circuitry, a number of studies have focused on their regulatory role in depression and cognitive dysfunction[66].

The expression of MRs was decreased in the hippocampus, inferior frontal gyrus, and cingulate gyrus in depressed patients[67,68]. In addition, neuroendocrine studies also indicated abnormal MR function in MDD[63]. Otte C *et al*[69] found that the administration of an MR agonist (fludrocortisone) in drug-free patients with depression effectively reduced cortisol secretion and improved their verbal memory and executive function. In MDD patients treated with escitalopram, fludrocortisone accelerated the treatment response by 6 d. Furthermore, *MR* gene variants[70,71] and haplotypes[72,73] have been associated with depression symptoms and stress-induced reward-related learning deficits, and MR haplotypes may be potential biomarkers for a subgroup of patients with atypical depression[73]. In addition, MR malfunction and abnormal DNA methylation level have been demonstrated in treatment-resistant depression, depression during pregnancy, and in adolescence[74,75]. In preclinical studies, the role of the MR in the regulation of HPA-axis activity, executive function, and memory performance has been well demonstrated. In contrast to the effect of GR antagonists on long-term potentiation (LTP), MR antagonists inhibited the LTP process, suggesting that the MR and GR have opposite effects on the adjustment of synaptic plasticity after stress exposure[76]. The results from transgenic mice with forebrain knockout or overexpression of *MR* confirmed the role of MR in learning and memory[77]. After loss of the *MR* gene in the forebrain, mice displayed an aberrant basal and stress-induced CORT secretion and deficits in learning and memory[78]. In contrast, overexpression of MR in the forebrain improved spatial memory and behavior performance[79].

Research on the role of MR in the pathogenesis of depression is still in its infancy, and its possible mechanism has not been fully explained. Chen *et al*[80] reviewed the possible mechanism of MR in regulating depression, learning, and memory from different perspectives, such as HPA-axis activity, 5-HT transmitter system, adult-neurogenesis, and inflammation. Considering that MR can participate in the regulation of other and immune-related diseases by activating NLRP3 inflammasome[81,82], whether the role of MR in the pathogenesis of depression is involved in inflammasomes and modulation of inflammasomes will be important research directions in the future.

ER

Given that the prevalence of depression in women is 2-3 times higher than that in men and changes in mood are simultaneously associated with estrogen levels[83], a potential role for estrogen in the pathophysiology of depression has generated substantial interest. It is well documented that estrogen can regulate neurotransmission, enhance the levels of serotonin and noradrenaline, and plays a vital role in emotion processing, cognition regulation, and motivation triggers[84,85]. The data from clinical and preclinical research show that estrogen is involved in modulation of depression and anxiety. For example, cumulative clinical studies found that menopausal declines in estrogen levels were associated with an increase in mood disturbances in women[86,87]. Moreover, premenopausal women with depression had lower levels of 17β-estradiol (E_2) than non-depressed women[88]. In rodents, ovariectomy, resulting in estrogen deficiency, induced an increase in depression and anxiety-like behavior[89] which was improved by E_2 replacement[90].

Estrogen plays its biological role mainly through activating ERs. The ERs including ERα (ESR1) and ERβ (ESR2) are members of a superfamily of hormone-regulated transcription factors, and regulate the gene transcription of estrogen by binding to specific DNA sequences[91]. Genetic variation in ERs may therefore modify estrogen signaling, such as altering binding efficiency and disrupting normal gene regulation, thus increasing susceptibility to developing depression in women. Ryan J *et al*[87] carried out a detailed review and pointed out that there was a significant correlation between *ESR1* gene polymorphism and severe depression in women. Preclinical research has demonstrated that ERα and ERβ agonists can reverse stress-induced depressive behavior and cognitive deficits[92]. However, the specific mechanism of ER in stress-induced depression remains unclear. Some studies have found that NLRP3 inflammasome activation mediates estrogen deficiency-induced depressive-like behavior and neuroinflammation in the hippocampus of mice[93]. In other inflammation-related diseases, such as endometriosis and breast cancer, the ER regulates the activation of NLRP3, which leads to inflammation[94,95].

AHR

AHR is a ligand-activated transcription factor which was first identified as a contaminant of the chemical herbicide Agent Orange[96]. However, AHR has been proved to be a crucial modulator of host-environment interactions in recent years, espe-cially for immune and inflammatory responses. As an NR, AHR is bound by co-chaperones Hsp90 and XAP that maintain its localization in the cytoplasm. After ligand binding, AHR is released from its co-chaperones and is transferred to the nucleus, where it forms a heterodimer with AHR nuclear translocator (ARNT) and binds to DNA to regulate target gene expression[97]. AHR can bind to many diverse ligands, including exogenous synthetic aromatic hydrocarbons [*e.g.*, benzo (a) pyrene], exogenous natural chemicals [*e.g.*, tryptophan (Trp) and norisoboldine], and endogenous ligands (*e.g.*, tryptamine and kynurenine)[98]. Specifically, compounds from the Trp metabolic pathway, especially the kynurenine pathway (~95% of Trp metabolism), provide many ligands for the AHR and play an important role in the regulation of immune and inflammatory responses. A large body of studies have shown that the AHR is associated with many diseases driven by immune/inflammatory processes, including MDD, asthma, multiple sclerosis, rheumatoid arthritis, and allergic reactions[97].

Increased kynurenine (KYN) production from Trp metabolism, mediated by indoleamine 2,3-dioxygenase (IDO), is a biomarker of immune dysregulation in depression [99]. Clinical and preclinical data have consistently shown an elevated KYN level with depressive behavior after immune disturbance. The activation of AHR signaling may play an important role in immune regulation. Preclinical evidence has shown that blocking the AHR can reverse KYN-induced monocyte trafficking, neuroimmune disorder, and depression-like behavior in mice[99]. Recent clinical studies have also confirmed that the AHR is related to the individual difference in plasma KYN concentration in MDD patients[100]. The AHR regulates the expression of Trp-2,3-dioxygenase 2 (TDO2) and IDO1/2, and downstream enzymes kynurenase and kynurene 3-monooxygenase (KMO). The results of *in vitro* cell culture showed that AHR knockdown resulted in a decrease of KYN concentration in the cell culture medium, which may be due to the increase in quinolinic acid, a downstream metabolite of KYN[97]. Quinolinic acid is a neurotoxic NMDA receptor agonist and contributes to MDD symptoms[100]. Although cumulative data have confirmed the regulatory role of AHR in depression-like behavior induced by an abnormal KYN metabolic pathway, the specific mechanism has not been clearly elucidated. A

significant result showed that AHR can regulate the activity of NLRP3 inflammasome by inhibiting the transcription of *NLRP3*[101]. The proposed model is as follows: Following engagement by AHR cognate ligands, it forms a heterodimer with ARNT in the nucleus, binds to the xenobiotic response element (XRE) regions located at the NF-κB site in the promoter of *NLRP3* and then inhibits NF-κB transcription activity, finally decreasing *NLRP3* transcription and subsequent inflammasome activation[101]. In view of the role of NLRP3 in the neuroimmune mechanism of depression, this may be the potential mechanism of AHR in regulating depressive episodes. In addition, the AHR acts as a potential crosstalk mediator between the adaptive immune system in the gut and gut microbiota-derived metabolites. Whether AHR has a certain role in the brain-gut axis dysfunction of MDD should be investigated in subsequent research.

PPARs

PPARs are ligand-activated transcription factors and members of the NR receptor superfamily. Three isotypes of PPARs have been identified, namely, PPARα, PPARβ/δ, and PPARγ[102]. Despite the three PPAR isoforms having a high degree of structural homology, they have distinct tissue distribution, ligand-binding properties, and functional roles. Endogenous and natural ligands of PPARs mainly include fatty acids and fatty-acid derivatives. PPARs translocate into the nucleus upon ligand binding, where they form heterodimers with the RXR and then bind to peroxisome proliferator response elements to regulate transcriptional target genes. The physiological characteristics of PPARα, β/δ, and γ and their role in other diseases have been extensively reviewed[103,104], and will not be elaborated here. Next, we will discuss the role of PPARs in depression.

PPARα

PPARα is distributed in many peripheral tissues which catabolize high amounts of fatty acids. In the CNS, PPARα is highly expressed in the basal ganglia, prefrontal cortex, thalamic nuclei, hippocampus, and ventral and tegmental areas[105]. In these regions, the distribution of PPARα in neurons is higher than that in glial cells. Recent research found that PPARα modulates the stress response, neurotransmission, neuroinflammation, and neurogenesis and plays an important regulatory role in some neuropsychiatric diseases, such as depression, post-traumatic stress disorder, and neurodegenerative diseases[106]. Preclinical studies found that knockout or overexpression of PPARα in rodent brain could imitate or reverse the depressive-like behavior induced by chronic stress. In addition, PPARα selective agonists (WY14643 and fenofibrate) have been associated with antidepressant effects in stress-induced depression models[107,108]. Some antidepressants, such as venlafaxine and fluoxetine, need PPARα to play an antidepressant role[109]. The antidepressant effect may be mediated by acting on the cAMP response element-binding (CREB)-mediated biosynthesis of brain-derived neurotrophic factor (BDNF)[109-111]. Some studies have also indicated that PPARα can modulate mesolimbic dopamine transmission and improve depression-related behavior[112]. Furthermore, N-palmitoylethanolamine, which stimulates PPARα, induced a dose-dependent antidepressant effect by engaging neurosteroid biosynthesis[113]. In summary, PPARα may play an important role in the pathogenesis of MDD and the effects of antidepressant medications, and it may be a new target for developing novel antidepressants.

PPARβ/δ

PPARβ/δ is the most widely expressed isoform in the brain, with particularly high levels in the hippocampus, entorhinal cortex, and hypothalamus[105]. Compared with the other two subtypes, PPARβ/δ showed a higher expression level in neurons, and had neuroprotective effects in some CNS disease models[114]. Recent studies have found that overexpression of PPARβ/δ in the hippocampus can inhibit depressive-like behavior induced by chronic stress in rats, which corresponds to a significant down-regulation of PPARβ/δ expression in the hippocampus when rats experience chronic unpredictable stress[115]. Subsequent studies have found that when PPARβ/δ is knocked down, rats show depressive-like behavior[116]. Similar to the antidepressant effect of PPARα, the CREB-BDNF pathway may also be involved in the antidepressant effect of PPARβ/δ. Furthermore, chronic stress can increase the expression of TWIST1, which will lead to mitochondrial damage and ATP deficiency by down-regulating PPARβ/δ expression, and eventually leads to depression-like behavior in mice[116]. How overexpression of PPARβ/δ and its agonists play an antidepressant role is still unclear.

PPARγ

PPARγ is highly expressed in the amygdala, dental gyrus, prefrontal cortex, ventral tegmental area, and basal ganglia[105]. Under normal physiological conditions, PPARγ can co-localize with neurons and astrocytes in human and mouse brain, but not with microglia. However, PPARγ can also be expressed in microglia when the functional status of microglia changes. PPARγ agonists have been synthesized for the treatment of metabolic diseases, especially dyslipidemia and type 2 diabetes mellitus, as well as non-metabolic diseases including neurodegenerative diseases, cancer, and inflammatory diseases due to their important metabolic regulation and excellent druggability[117,118]. Compared with the above two subtypes, the relationship between PPARγ and depression has been more widely recognized, and clinical trials on the antidepressant effects of PPARγ agonists are in full swing. Some gratifying results have been found and were well reviewed[117].

In conclusion, all isotypes of PPAR may participate in the pathophysiology of depression, and even antidepressants based on PPAR agonists have been developed. However, how PPARs play an antidepressant role seems unclear, although some studies have shown that this occurs by regulating the biosynthesis of BDNF and regulating the 5-HT neurotransmitter system. Activation of PPARs inhibits the activation of inflammasomes (in particular NLRP3) and the release of inflammatory cytokines, which is similar to the changes in patients with depression and in depressive models[119,120]. Therefore, whether and how PPARs play an antidepressant role by regulating the inflammatory response will be an important future research direction. In fact, some studies have found a link between them. Liu *et al*[121] found that oridonin, mediated through the PPARγ receptor signaling pathway, modulated excitatory alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the prefrontal cortex, and showed fast and significant antidepressant efficacy. In addition, Song *et al*[122] found that, astragaloside IV, which exhibited PPARγ agonist activity, ameliorated stress and neuroinflammation-induced depressive-like behaviors *via* the PPARγ/NF-κB/NLRP3 inflammasome axis in mice. Apigenin exhibits antidepressant-like effects by inhibiting NLRP3 inflammasome activation through the upregulation of PPARγ in rats with CUMS[123]. Moreover, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease, PPARβ/δ agonist alleviates NLRP3 inflammasome-mediated neuroinflammation[120].

CONCLUSION

Given the relatively low overall response rates and the wide range of 'adverse' events associated with current antidepressants, there is an urgent need for novel therapeutics to treat specific underlying disease mechanisms that are not addressed by the antidepressants targeting the serotonergic and/or noradrenergic system. Hopefully, the modulation of NRs with hormones and metabolites may become one of the key endocrinologic mechanisms for the development of novel therapeutics to increase the likelihood of therapeutic efficacy. Here, we reviewed the regulatory role of NRs (including the GC, MR, ER, AHR, and PPAR) in inflammasome activation and the pathophysiology of depression (Figure 1). Indeed, a major breakthrough in the pathophysiology of depression was the discovery that DAMPs and PAMPs activate inflammasomes, which enhance caspase-1 activity, and subsequently inhibit excitatory AMPA receptor synaptic plasticity in the brain circuitry to change mood-associated behaviors[124,125]. Cumulative studies have shown that activation of the NRs may directly change the activity of inflammasomes to modulate the levels of mature forms of caspase-1 and IL-1β. Caspase-1-mediated programmed cell death and surface stability of the AMPA receptor in the hippocampus, are essential for depression-like behavior[125]. Current data suggest that direct modulation of NRs may offer new opportunities to mitigate depressive disorders. However, several directions are warranted for future studies: (1) To identify more NR activators for the treatment of MDD; (2) To address the detailed mechanism of how NRs modulate inflammasomes; and (3) To perform clinical trials to prove the role of NR modulators in the treatment of MDD. These NR modulators can be safely used in combination with currently available antidepressants to simultaneously target multiple disease mechanisms and increase the likelihood of therapeutic success.

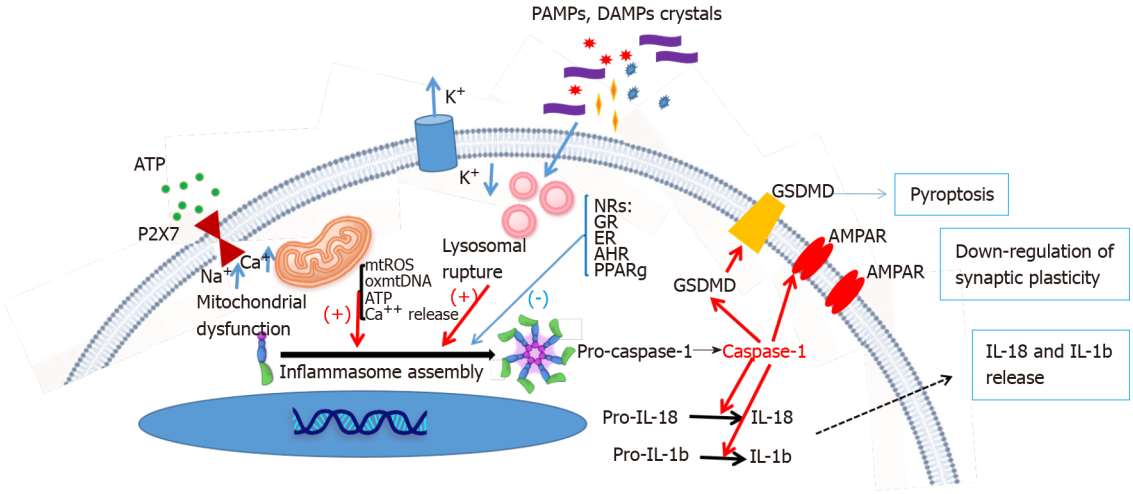


Figure 1 Inflammasome activation in the pathophysiology of major depressive disorder - roles of the nuclear receptors. NLRP3 inflammasome activation, which includes canonical and noncanonical activation pathways, is induced by a number of pathogen-associated molecular patterns and danger signaling molecules patterns. The canonical activation pathway involves stimulation-mediated activation signals such as ion fluxes, lysosomal rupture, mitochondrial dysfunction, and so on. Mitochondrial dysfunction leads to the production of mitochondrial reactive oxygen species, damaged mitochondrial DNA, and calcium release from the mitochondria, and all these changes facilitate the assembly of inflammasomes. Activation of the inflammasome causes caspase-1 activation, leading to the maturation and release of interleukin (IL)-1/IL-18 and pyroptosis. In addition, caspase-1 modulates the membrane stability of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which leads to the down-regulation of AMPA receptors at the synapses. Nuclear receptors inhibit the assembly of NLRP3 inflammasome, which will finally protect the excitatory AMPA receptor synaptic activity and contribute to the antidepressant mechanism of the nuclear receptor activators. ROS: Reactive oxygen species; PAMPS: Pathogen-associated molecular patterns; DAMPS: Danger associated molecular patterns; GSDMD: Gasdermin D; AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; IL: Interleukin; NRs: Nuclear receptors; GR: Glucocorticoid receptor; ER: Estrogen receptor; AHR: Aryl hydrocarbon receptor; PPAR: Peroxisome proliferator-activated receptor; ATP: Adenosine triphosphate.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1206-1227

DOI: 10.5498/wjp.v11.i12.1206

ISSN 2220-3206 (online)

REVIEW

Review of barriers and interventions to promote treatment engagement for pediatric attention deficit hyperactivity disorder care

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Author contributions: Baweja R conceptualized this paper, draft the initial manuscript, reviewed and revised the manuscript; Soutullo CA contributed in the initial manuscript, reviewed and revised the manuscript; Waxmonsky JG conceptualized this paper, contributed in the initial manuscript, critically reviewed and revised the manuscript; All authors approved the final manuscript as submitted and agree to accountable for all aspect of the work.

Conflict-of-interest statement: Soutullo CA reports non-personal research funds from Texas Child Mental Health Care Consortium (Youth Depression & Suicide Network) SB11, Lundbeck and Janssen; is a consultant and advisory board member of Editorial Médica Panamericana, EUNETHYDIS (European Network on Hyperkinetic Disorder), NeuroTech Solutions Ltd-Israel, Limbix -United States and Shire - Spain; received speaker's bureau fees from Bial- Portugal, Medice - Germany, Rubio-Spain and Shire-Spain, and royalties from Editorial Médica Panamericana - Spain;

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a common and impairing behavioral health disorder, impacting over 5% of children worldwide. There are multiple evidence-based pharmacological and psychosocial treatments for ADHD, and greater service utilization is associated with improved acute and long-term outcomes. However, long-term outcomes are suboptimal as multimodal treatments are often not accessed and most care ends prematurely. This narrative review discusses barriers to engagement for children and adolescents with ADHD and their families as well as interventions to overcome these barriers. Families face a variety of structural and attitudinal barriers, ranging from cost and access to stigma and low self-efficacy to successfully implement change. There are multiple interventions that may enhance engagement with ADHD care including psychoeducation, integration of behavioral services in general medical settings, telehealth as well as specific adaptations to existing ADHD treatments, such as the use of motivational interviewing or shared decision making. Integration of behavioral health into general medical settings and telehealth have been found in controlled studies to increase access by reducing both structural and attitudinal barriers. Adding motivational interviewing, shared decision making and other engagement interventions to evidence-based ADHD treatments has been found to reduce attitudinal barriers that translates into improved participation and satisfaction while enhancing outcomes. However, little is known about how to promote extended engagement with ADHD services even though a chronic care model for ADHD is recommended.

Key Words: Attention deficit hyperactivity disorder; Treatment engagement; Barriers; Interventions; Children; Adolescents

Waxmonsky JG has received research funding from Supernus, and Pfizer, is a consultant for Purdue Pharma, Intracellular Therapies; Baweja R reports no conflicts of interest related to the subject of this article.

Country/Territory of origin: United States

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: March 26, 2021
Peer-review started: March 26, 2021
First decision: June 17, 2021
Revised: June 20, 2021
Accepted: October 25, 2021
Article in press: October 25, 2021
Published online: December 19, 2021

P-Reviewer: Thummer RP
S-Editor: Liu M
L-Editor: A
P-Editor: Liu M

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Core Tip: Assessment of families' motivation for care at treatment initiation and recurrently over the course of treatment, especially during times of increasing stress and declining functioning, is essential to promote sustained engagement. Aspects of motivation that predict sustained engagement include desire and readiness for care, treatment preferences, self-efficacy to access and implement the selected treatment and perceived barriers to the treatment. Integrating services into trusted medical settings to reduce stigma, telehealth to reduce the burden of care, shared decision making to promote autonomy, psychoeducation about treatment options and how attention deficit hyperactivity disorder impacts current functioning and motivational interviewing can be employed to promote engagement.

Citation: Baweja R, Soutullo CA, Waxmonsky JG. Review of barriers and interventions to promote treatment engagement for pediatric attention deficit hyperactivity disorder care. *World J Psychiatr* 2021; 11(12): 1206-1227
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1206.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1206

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common and impairing behavioral health (BH) disorder, impacting over 5% of children worldwide[1]. Impairment often persists into adulthood leading to recommendation to treat ADHD with a chronic care model[2,3]. Multiple evidence-based pharmacological and psychosocial interventions exist for ADHD[3-5]. In the United States, most children diagnosed with ADHD receive some treatment for it with 5% of school-aged children prescribed ADHD medication. In other countries rates of ADHD medication use in children are often below the reported prevalence rates, varying from 3% (France, Japan) to 5% (Iceland)[6]. Across countries, multimodal treatment and rates of any counseling services rates under 50%, even in countries where treatment guidelines prioritize initial treatment with behavioral interventions[7-11]. In the United States, most care starts in primary care, with primary care clinicians (PCCs) being the most common provider of ADHD services[12]. However, a number of specialty medical providers treat ADHD and schools offer a variety of therapeutic supports[7,12].

Most countries in the European Union and the United Kingdom have universal access, National Health Systems, funded by the State *via* taxpayer deduction on the worker´s paychecks. These systems usually also cover the rest of the family, including children, even if the parents are not working at the time. There are different levels of coverage within the European Union especially for medication and counseling services leading to appreciable variations in ADHD care across national boundaries. Access to specialists varies widely across countries, as do the administrative requirements to get to specialty care. Initial assessment and diagnosis can start in general or specialty settings[13,14]. For example, in the United Kingdom, patients with possible ADHD are referred to a Child Psychiatry and Psychology Evaluation Unit that performs a comprehensive medical, psychiatric, psychological, school and social evaluation that may take several months to be completed. In Italy, there are less than 10 Pediatric Neuropsychiatry Outpatients Units that are allowed to prescribe methylphenidate, creating substantial waits for a country with a population of 60 million. In Spain, Child and Adolescent Psychiatry is not recognized as a specialty yet. Pediatricians can start medication, and can refer to either Pediatric Neurology (usually younger children and those with medical comorbidity as epilepsy or neurodevelopmental delays) or Child Psychiatry Units usually staffed by general psychiatrists with variable levels of expertise.

CARE OUTCOMES

Despite well-established assessments and evidence-based and available treatments,

long-term outcomes are suboptimal across countries[2,15,16]. One major challenge to achieving optimal long-term outcome is treatment engagement. Initiating care can be a challenge as many referred families fail to access any care[17]. When initiated, care is often interrupted or quickly discontinued. In both primary care and specialty care settings, utilization rapidly declines over the first year of treatment[18-20]. In the United States, care for nearly 60% of publically insured youth does not meet federal guidelines for frequency of reassessment[21]. Similarly, low rates have been found in Australia, with only 28% children diagnosed with ADHD receiving any services in the past 6 mo[22] and sizable percentage of children with ADHD in United Kingdom are not receiving treatment[23]. When stopping care, most patients still exhibit appreciable impairment[21] and many who experience interrupted care never return[24].

Numerous studies have shown rapid declines in ADHD medication usage over time. In both Europe and the United States, over half of children stop medication within 6 mo[25,26]. Rates of treatment utilization for CNS stimulants continue to decline after year one[27]. By the end of adolescence, only 10% of youth with ADHD are using medication even half of the time[2]. Even short-term medication adherence is challenging as over one month, only about 40% of children take every dose of medication prescribed[28].

Engagement with counseling services face similar if not greater challenges to those for medication treatments. In the United States, many families never access counseling, as these services are less likely to be available in general medical settings than medication treatments[29,30]. Up to half of referrals for counseling services for ADHD fail to translate to any treatment[31] as families often stop care when referred to external BH providers[18]. For those who do connect, care often ends prematurely[20, 32]. In a review of insurance claims data in the United States from 2008-2014, under half of families with a child diagnosed with ADHD accessed any billable psychosocial services. Among families accessing any treatment, only half attended 4+ sessions over any 12-month period[10]. Other reports from the United States[33], other western Countries and across the globe[34,35] show similarly low rates. Multimodal treatment is recommended for children[3,5], most desired by caretakers[36] and is most likely to optimize functioning especially for low-income youth[4,37,38]. However, combined treatment is particularly challenging to establish and maintain, with only 20%-33% youth accessing both counseling and medication in the same year[10,39].

While challenging to achieve, greater service utilization is associated with improved acute and long-term outcomes[16,20,40], especially in primary care where treatment usage rates are particularly low[31,41,42]. Therefore, efforts to promote sustained utilization may be one means to enhance long-term outcome. Current ADHD guidelines[3,5] recommend engagement efforts that begin when care starts. They advise measuring progress towards personal goals along with symptoms using scheduled assessments, while promoting families to be informed advocates in their child's care. This review will discuss identified barriers to engagement with pediatric ADHD care and interventions to overcome these barriers (Figure 1).

Existing literature was ascertained in the English language, published until March 2021, using searches of MEDLINE and PsycInfo for the following categories: ADHD, children, adolescence, engagement, adherence, methylphenidate, amphetamine, pharmacotherapy, drugs, CNS stimulants, nonstimulants, medication, psychotherapy, psychosocial intervention, counseling, parent training, behavioral therapy, and multimodal treatment. References from identified articles were reviewed to ensure that all relevant papers were included.

BARRIERS OF TREATMENT ENGAGEMENT

Numerous barriers have been identified to sustained engagement with pediatric mental health services. These can be classified as structural such as long waiting lists, limited hours of operation or cost and attitudinal, which encompass a variety of perceptions about mental health and its treatment. These include beliefs that mental health disorders do not exist or cannot be improved, to stigma about receiving a diagnosis or treatment for it.

Structural barriers

A variety of physical, geographical, financial and access barriers have all been found to impede ADHD care in over half of families of a child with the disorder[19,43]. Geographical barriers such as distance to a provider have been found to be particularly relevant to BH care, especially in rural areas where there are few specialty

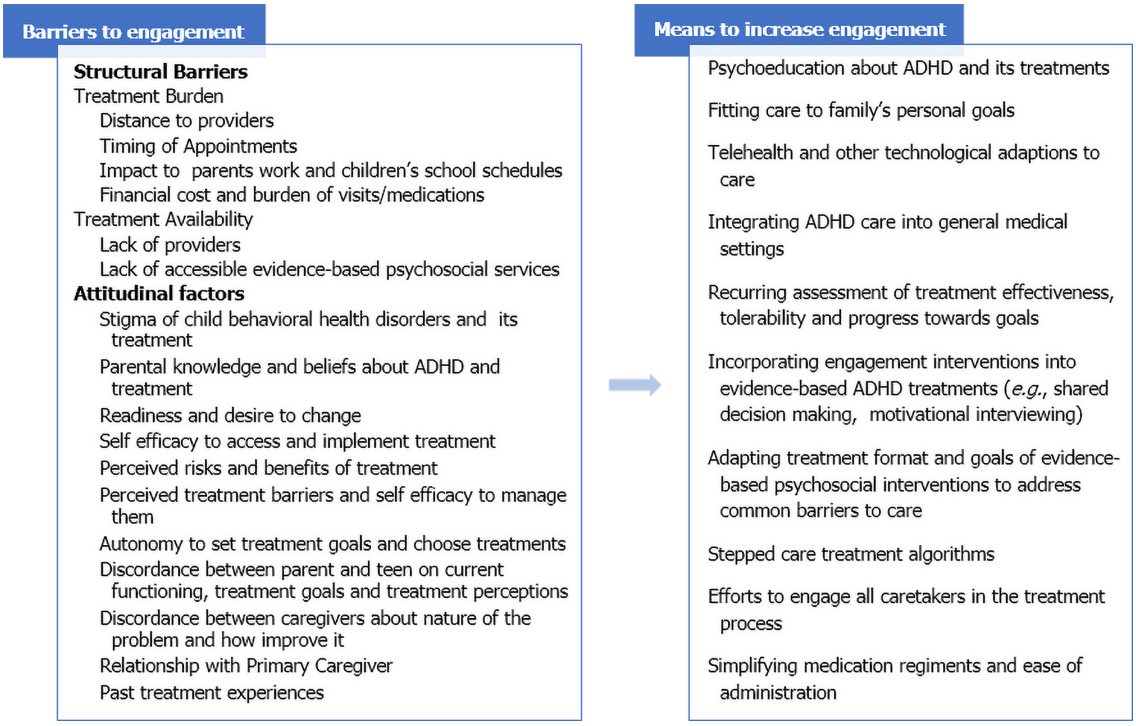


Figure 1 Barriers and interventions to promote treatment engagement for attention deficit hyperactivity disorder. ADHD: Attention deficit hyperactivity disorder.

treatment options[44,45]. These structural barriers exist to varying degrees in different healthcare models. Despite having a Universal National Health System in the European Union and the United Kingdom, there are still structural barriers to ADHD care. In a study from Taiwan, families who are able to access specialty care appear more likely to stay in care than those getting care in general medical settings[46]. Mostly problematic is the limited availability of Child Psychiatrist and Child Psychology providers. That lack of availability generates sizable travel times, long waiting lists and suboptimal reassessment schedules.

Financial cost is a commonly cited structural barrier to the treatment for ADHD[22,47,48]. In the United States, treatment coverage can vary widely by insurance plan, creating substantive financial barriers even for those with health insurance. For example, behavioral interventions for children are not covered as an essential benefit under the Affordable Care Act[49]. Bussing *et al*[50] reported that 38% families reported cost as a main reason for not to pursue treatment, while rates of medication usage are positively correlated with income[51]. Lowering costs has been found to improve treatment adherence for ADHD care[52]. In Europe, ADHD care is not universally covered by public insurance[53]. Even in countries with universal healthcare coverage that encompasses ADHD services, the long wait times have created a private healthcare market where cost of services can be an appreciable barrier. ADHD significantly increases a family's medical cost, more than many other chronic medical conditions. ADHD in children can also reduce parents' capacity to attend work. Parents of ADHD youth are more likely to have ADHD themselves[54], which is associated with reduced educational achievement and earning potential[55]. Parental psychopathology may also impact the ability to engage with and implement BH services for their children[56,57].

When socio-economic status (SES) has been formally examined as a treatment barrier, the data is mixed. Lower SES is associated with less likely to engage and adhere to ADHD treatment[20,50]. In the United States, public *vs* private insurance is associated with higher rates of counseling services[7,10,12]. In the Multimodal Treatment of ADHD study (MTA), SES moderated adherence to behavioral and combined treatment, but not medication[19]. Other analysis has observed that SES is inversely associated with medication adherence[58]. In the United States, differences in treatment utilization across race/ethnicity are diminished when sociodemographic variables are taken into consideration[59].

Taking ADHD medication several times per day can be an appreciable challenge[28,48,60,61]. Extended-release versions that only require once daily dosing are associated

with improved adherence[25], but even youth using extended-release preparations struggle with adherence[40]. Furthermore, extended-release medications often come with higher costs forcing families and prescribers to balance between finances and convenience[62]. More than 40% stimulants medication prescription for ADHD require prior-authorization in countries where they have managed care[63] creating additional barriers to more convenient and palatable care. In other countries, office visits are required to adjust the dose and the long waits between appointments can create a sizable impediment to timely dose optimization.

Attitudinal factors

Uptake of care can be low even when it is readily accessible[38,42,64,65]. Attitudinal barriers[66] more strongly predict BH utilization than treatment type or provider, especially for low-income families[38]. Parents are the main agent of change for a child's BH, making parental attitudes, perceptions and preferences important variables to assess when trying to promote engagement[67]. Parental knowledge and beliefs regarding ADHD and its treatment affect decisions to both initiate and continue with care[68]. Parents who feel that they have little influence over their child's behavior or that their child is choosing to misbehave are less likely to engage in counseling interventions for ADHD[69,70]. Parental attributions for a child's behavioral problems appear to be particularly robust predictors for fathers who are more likely to engage in care when they feel they can influence their child's behavior[71].

Parental views on ADHD medication vary widely, ranging from unacceptable to the preferred treatment[27,72]. Parents who view their child's symptoms as a medical disorder are more likely to initiate medication[72]. In contrast parents who view ADHD as age normative fluctuations in behavior[48,73] are less likely to use medication. Parental knowledge about ADHD and medication treatment is predictive of medication acceptance and usage[19,34,74]. While having more knowledge may increase willingness of parents to initiate medication, it does not reliably predict medication adherence or long-term usage and may reduce interest in evidence-based psychosocial treatments[34,75]. The degree of symptom reduction also does not predict adherence. Rather parents appear to weigh the perceived risks of medication usage *vs* its perceived benefits while deciding how often and for how long to use medication[24]. Pretreatment preferences for treatment modality do not reliably predict uptake of counseling services as most adults rate psychosocial treatments as palatable[76]. Initial treatment decisions also impact future care. Past medication use is one the most robust predictors for future medication use for ADHD, while use of medication appears to lower motivation for future counseling services even when impairment persists, both in clinical trials offering free care[77] and in routine care[10].

There are meaningful differences in treatment utilization across racial/ethnic groups. Black children are less likely than White children to use medication, but more likely to utilize counseling. Hispanic families are less likely than White non-Hispanic families to utilize counseling and medication. However, rates of medication are increasing over time amongst families of different races and ethnicities, particularly for Hispanic families[78,79]. Parental health beliefs about ADHD also appear to be influenced by race and ethnicity. Non-Hispanic White families are more likely to report greater knowledge about ADHD, more likely to view it as a medical disorder and more likely to view medication as safe than Black or Hispanic families. Moreover, Black and Hispanic families are more likely to report side effect concerns regarding ADHD medication and expect less benefit from medication[80-84]. In contrast to White Non-Hispanic families, increasing parental knowledge about ADHD in Hispanic families is associated with increased odds to utilize counseling but not medication[75].

Parents' perception about the impact of the child behaviors on parental and family functioning influences decision to pursue, accept and persist with treatment for ADHD[19,22]. For example, parents who perceive their child's behavior to be negatively affecting their career, are more likely to seek treatment[19]. The child's level of current functioning as well as the impact of treatment on their functioning appears to be particularly relevant for decisions regarding when to use medication for Hispanic families[75]. While increased parental stress may drive treatment seeking, persistently stressed parents are prone to disengage care[84]. Similarly, children with comorbid disorders, especially other externalizing behavioral disorders, may be more apt to present for treatment but experience higher rates of premature dropout[19].

Stigma related to child mental health and specifically to ADHD have been identified as sizable barriers to initiating treatment[81,85]. Unfortunately, there is continuous to be an appreciable stigma regarding having a child with ADHD and surrounding treatment for ADHD[74]. In the MTA study, stigma was a common reason for discontinuing medication[24]. However, failure to treat also increases the risk of being

stigmatized as Singh *et al*[86] observed youth are more likely to experience stigma due to their symptomatic behaviors than to disclosing medication use. Parental perceptions of their relationship with their child's healthcare provider influences decisions to initiate ADHD medication and can counteract stigma concerns, especially when the primary care provider is also managing ADHD[72]. However, providers do not always talk with families about their goals and preferences for the treatment for the ADHD[87]. Opinions of others also impact care decisions as parents are most likely to engage in a treatment when medical advice meshes with feedback from family and friends[88].

Attitudinal factors may also influence national healthcare policy. The acceptance of biological psychiatry may be a barrier to both diagnosis and treatment. For example, in France (population 65 million), where there is still a strong psychoanalytic tradition and the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases nomenclatures are not widely accepted, there are only a few approved ADHD medications and very limited specialty treatment centers[89,90]. Spain (population 47 million), where Child and Adolescent Psychiatry is still not a recognized medical specialty, has just one child psychiatry fellowship program at the University of Navarra[91].

Patients and families value treatment choices and typically will access more preferred treatments. Treatment goals have also been found to predict which type of ADHD intervention is used. Parents prioritizing academic goals are more likely to use medication, while those with behavioral goals lean towards psychosocial treatments [65]. However, for ADHD, it does not appear that families access only preferred treatments. Most treatment seeking families rate psychosocial treatments as most palatable but medication is more commonly used in the United States, even in young children[7,10,12,76]. Using easily accessible but unpalatable treatments has been identified as one cause for poor sustained utilization of ADHD services[40]. However, even caretakers preferring psychosocial treatments often fail to persist with treatments [76] suggesting using preferred treatments is insufficient to produce sustained engagement.

Perceptions about the burden and safety of treatment also predict utilization. Many parents report hesitancy to use ADHD medications due to side effect concerns[92,93]. Side effects are also one of the most common reasons for discontinuing ADHD medication reported by parents and adolescents[24,93]. The most common side effect concerns related to changes in sleep, appetite, mood and perceived risk of addiction [94]. For counseling services, the perceived intensity and burden of care are relevant factors as parental motivation for care is one of the most robust predictors of counseling dropout and treatment response[20,95-97].

Self-efficacy is another variable impacting engagement with ADHD care, especially for counseling where parents are the primary agents of change for their child. Parents of children with ADHD report increased parental stress and reduced self-efficacy[64, 98]. In fact, parental self-efficacy mediates the relationship between parental ADHD and increased parenting stress[99]. Low self-efficacy in mothers and fathers predict poor treatment outcome in children with ADHD. In the MTA study, parents with low self-efficacy had difficulties in implementing behavioral plans, consistently administering medications, and reported more stress[100].

Engaging all caretakers improves treatment utilization and durability[101]. Engaging fathers can be particularly challenging as ADHD is associated with higher rates of divorce, single parenting and separated households and fathers are less likely to present for office-based care[102,103]. Perceived criticism by the other parent is a major risk factor for dropout for fathers[104], so parental conflict can present a major barrier to sustained care. Single parent families also face unique challenges to accessing, persisting and implementing ADHD treatments including higher rates of parental psychopathology and smaller social support networks[19,102].

For adolescents to initiate and persist with a treatment, the patient and parent must recognize and agree on a problem, desire better functioning and believe that the treatment is an acceptable means to achieve a goal that they all feel capable of implementing and accessing. Adolescents prioritize autonomy to set their own goals and the freedom to pick treatments that match their goals[105,106]. All these aspects of motivation have been found to predict utilization of pharmacological and counseling services for ADHD[40,74,107]. Self-awareness about functioning is often poor in adolescents with ADHD and has been found to correlate with medication adherence [108,109]. Adolescents' limited insight of their current impairments often leads to parents and teens disagreeing about the need for treatment, and the level of discordance predicts treatment persistence[24,107]. Higher trait antagonism in adolescents also predicts reduced treatment uptake[110]. Not surprisingly, treatment

adherence, especially for medication, declines rapidly over adolescence. Across countries, medication use drops significantly during adolescents[2,111]. Typically, the decision to stop is driven by the adolescent with the most common reason for discontinuation being the adolescent felt medication was not needed anymore. However, parents and teachers continue to report high rates of impairment in adolescents stopping medication. Therefore, it appears that adolescents' limited self-awareness is an appreciable barrier to both starting and continuing with ADHD care[24,107,108]. Side effect concerns, followed by stigma are the next most common reason reported by adolescents for stopping medication[24,110].

INTERVENTIONS TO PROMOTE TREATMENT ENGAGEMENT

Psychoeducation

As parental knowledge and perceptions of ADHD influence decisions to start ADHD care, psychoeducation has been explored as a means to improve treatment uptake. For example, more extended ADHD assessments are associated with increased parental willingness to start medication[112]. The largest study assessing this issue was set in the United States and examined the efficacy of a neuro-educational intervention in 658 families of children with ADHD whose parents had either discontinued or declined medication for their children following their initial diagnosis of ADHD. At study entry, lack of direct testing of their child's attention span and side effect concerns were the most commonly reported barriers to treatment. The study intervention consisted of a semi-structured diagnostic interview supplemented with two objective measures of attention and impulse control over 3 sessions with last session dedicated to a systematic review of findings with the family along with psychoeducation about ADHD and its treatment. This visit was run using a manualized format which included information about the causes of ADHD, rationale for medication use, strategies for reducing side effects, tips for improving sleep and diets, importance of school support and accommodation and practical strategies to address common behavioral, emotional and social problems during early phase of medication treatment. Following this brief diagnostic and educational intervention, over 70% of parents started medication for their children with treatment rates increasing to over 95% by month 6. At the 2-year follow-up, 95% were still taking medication for ADHD [113]. However, other studies have not observed associations between psychoeducation and persistent treatment engagement[34,75,114], and a systematic review found that patient education alone has limited impact on medication adherence in youth [115]. In a small study set in Spain, adding a brief nurse run psychoeducation intervention to medication treatment led to lower mean doses with no loss of efficacy *vs* medication alone[116]. Therefore, psychoeducation may also be a means to improve treatment tolerability.

Integrated care

Families report greater comfort in primary care settings *vs* BH settings[117,118]. However, specialty care is associated with increased contact and more frequent medication adjustments. Integration of BH services into primary care is one means to accomplish increased contact with patients that predicts greater service utilization[41], especially in countries where generalists provide much of the ADHD care[7,119]. Most models employ two main techniques: Embedding specialty BH providers in primary care to offer counseling services and training primary care providers to employ systematic medication pathways for ADHD supported by remote child psychiatrists.

One of the first randomized trials of an integrated care ADHD intervention was published by Kolko *et al*[120], where 163 children were randomly assigned to nurse-administered intervention or to enhanced usual care (diagnostic assessment, recommendations, and facilitated referral to a specialty mental health provider in the community). The nurses completed an extensive training period and received ongoing supervision from specialists for the study duration. The core components of the intervention were: in office application of a menu of evidence-based counseling interventions, school consultation, case coordination and crisis management. The intervention arm was more likely to receive and complete mental health services, reported fewer barriers for services, more satisfaction, and were more likely to meet personalized treatment goals even though symptoms levels did not differ between groups[120]. A second similarly sized randomized controlled trial (RCT) of the intervention across 4 primary care sites using masters level care managers produced similar findings as well as greater overall improvement on the Clinical Global

Impressions Scale[121]. A more recent larger RCT of over 300 youth from 8 practices *vs* enhanced usual care (psychoeducation and care coordination services) found that the intervention led to greater rates of treatment initiation and completion, as well as larger changes in internalizing and externalizing symptoms, parental stress and satisfaction and primary care provider ADHD care competencies[122].

In a randomized comparative effectiveness trial, families of children being evaluated in primary care for ADHD (N: 156, ages 6-12), received care management with decision support using a collaborative care model and were randomized to enhanced care *vs* basic care. All treatment occurred in the primary care setting using care managers without a formal BH background, and families were recruited from low-income neighborhoods. Care managers in the enhanced care arm were trained in both motivational interviewing (MI) and parent management techniques to help parents identify and initiate ADHD care, address their own mental health concerns and improve their child's behaviors. In the enhanced arm, half of the families attended the primary care-based parenting intervention and 72% initiated medication for ADHD in their children. For the entire sample, there was no difference between basic and enhanced arm on means changes in scores for inattention, hyperactivity/impulsivity, oppositionality and social skills at both 6 mo and 12 mo of follow-up. However, after 12 mo, the enhanced arm experienced greater improvement among children with ADHD consistent presentations, with moderate to large effect sizes (0.57 for hyperactivity/impulsivity, 0.55 for oppositionality, and 0.69 for social skills)[42].

In a quasi-experimental design, Power *et al*[123] compared a multimodal primary care-based intervention to treatment as usual enhanced by a psychoeducation intervention. The Partnering to Achieve School Success (PASS) included family engagement strategies, behavioral therapy targeting the whole family, school consultation using principles of trauma-informed care. It was compared to treatment as usual supplemented with parent education and support groups. PASS was associated with greater changes in objectively measured negative parenting behaviors (ES = 30) and larger changes in child impairment (ES = 35) but not symptom scores [123].

Use of technology to promote engagement

Technology has also been used to enhance ADHD care through creation of specialized databases that prompt providers when and how to collect critical information such as parent and teacher ratings of ADHD symptoms and side effects[41]. Other technological advancements such as text message reminders from electronic medical records for when to take medication have increased adherence in adults with the disorder [124]. A recent review on telemedicine in the management of ADHD concluded that telemedicine is well accepted and valued by clinicians, caregivers, and educators. Use of telemedicine was also associated with improved outcomes although the results were limited by the small number of studies, most of which did not employ a control arm[125].

Telehealth services have also been used to reduce the structural barriers to integrating BH into pediatric primary care. The Children's ADHD Telemental Health Treatment Study randomized families of children with ADHD to one of two different telehealth delivery models in a predominantly rural area[126]. In the direct care telehealth intervention arm, participating families received 6 medication sessions over 22 wk by child psychiatrists *via* telehealth and parent behavior training, provided in person by community therapists who were supervised remotely. The Control arm received treatment from PCCs augmented with a telepsychiatry consultation from study psychiatrists. Children in both service models improved but those in the direct care telehealth arm experienced greater reductions in symptom scores and impairment [127].

A European study examined the efficacy of a behavioral parent training administered *via* telehealth in children already treated with CNS stimulants. The RCT compared the telephone-assisted self-help (TASH) intervention to routine clinical care. TASH did not separate on the primary outcome of parent rated impairment but group differences were seen on externalizing symptoms and negative parenting behaviors. Parents also expressed high satisfaction with the program, but completion rates were higher for families with a greater educational level and fewer additional stressors[128].

Interventions specifically targeting engagement

Several evidence-based psychosocial interventions for ADHD have incorporated formal engagement interventions to promote treatment uptake. For pediatric BH, engagement interventions have greater impact than those only addressing structural barriers[129]. These interventions target multiple aspects of motivation, including

desire and readiness for care, self-efficacy, treatment goals and preferences and planning for potential care barriers that all predict counseling and medication use and efficacy[65,74] and treatment persistence[20,24,95]. MI is the most commonly employed engagement intervention in pediatric ADHD treatments. It is a collaborative conversation designed to strengthen a patient's desire to change[130,131]. MI has been applied in medical and BH settings with moderate effects for improving a range of outcomes[132,133]. The other common components of these engagement interventions are a family interview to identify goals, a strengths-based assessment to promote self-efficacy, identify areas of need and a feedback session emphasizing discrepancies between current and desired functioning. These programs are often tailored to a specific population prone to greater challenges engaging with ADHD care, such as adolescents, fathers or single mothers.

In a study among single mothers of children with ADHD, participants were randomly assigned to an enhanced behavioral parent training program-the Strategies to Enhance Positive Parenting (STEPP) program or a traditional behavioral parent training program. The STEPP program (nine 21/2 h session) focused on enhancements to the format, delivery, and content of traditional parent training programs including: (1) An enhanced intake procedure to addresses practical barriers for participation in treatment, define realistic expectations from treatment, and identify attributions related children's behavior that promote parental efficacy; (2) Programming to improve social support for parents; and (3) A systematic problem-solving skill. Both arms led to improvements in child behavior but STEPP resulted in better attendance, participation and satisfaction[102]. COACHES (Coaching Our Acting-out Children: Heightening Essential Skills) is a behavioral parenting program designed for fathers that packages evidenced based techniques into a youth sporting event. During the first hours, fathers learn how to implement effective parenting strategies, while children practice soccer skills combined with a contingency management approach for appropriate behavior. During the second hour, the parent and child groups join for a soccer game, where fathers practice learned parenting strategies and get live feedback from therapists. COACHES was associated with better attendance and greater change in parenting behaviors and children's problem behaviors than standard behavioral parent training[134].

The STAND (Supporting Teens' Academic Needs Daily) program was designed to promote adolescents and parents in partnering to improve the teen's academic and home functioning. The first two sessions employ MI to aide parents and teens in identifying mutually agreeable goals and therapeutic techniques they will use prior to starting any specific treatments. STAND has been found to significantly improve adolescent functioning under randomized conditions, with parents and adolescents reporting high satisfaction, credibility and therapeutic engagement[108]. STAND has also been administered *via* videoconferencing with acceptable therapeutic alliance, treatment fidelity and effects[135]. When applied by community therapists, STAND led to increased parent participation and satisfaction *vs* treatment as usual. No differences in adolescent attendance or satisfaction were seen but STAND was associated with increased rates of starting or restarting ADHD medication *vs* treatment as usual[136].

Hamrin *et al*[137] used MI to improve medication adherence in 48 adolescents with mood disorders. The trial was set in specialty offices with psychiatrists applying MI with good fidelity during medication management visits. There was significant improvement in objectively measured medication adherence over a 30-d period (d = 0.65). While this trial did not require ADHD for entry, half of the sample had comorbid ADHD, and there was no evidence of reduced efficacy in those with ADHD *vs* those without it.

In Europe, where treatment of ADHD largely occurs in specialty settings[14], standardized care pathways have been developed for these settings. One example is the Dundee ADHD Clinical Care Pathway in Scotland[138]. It has standardized protocols for four stages derived from the NICE guidelines[5]: Referral and pre-assessment, assessment, initiating treatment and continuing care. Patients are referred to the program with initial screening conducted by nurse specialists who gather structured parent and teacher ratings prior to direct assessment, which focuses on functional impairments in the child and the level of family functioning. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children for DSM-IV--Present and Lifetime (KSADS-PL) is used for diagnostic determination. The assessment concludes with the family meeting with a senior clinician to review results. Initial treatment offerings are stratified by patient age with families of children under 6 referred to evidence-based behavioral parent training programs and those over 6 offered medication. A 4-wk dose optimization protocol is used for medication, prefer-

encing methylphenidate products. It consists of 3 to 4 visits that can be remote or in person with structured rating scales from parents and teachers used to titrate to optimal effect. Standardized definitions of meaningful response are used to determine if the initial treatment choice should be maintained or switched. Once optimized, nurse visits occur every 6 mo that measure adherence, stigma, other care barriers and functioning at home, school and with peers. Behavioral interventions are offered targeting identified impairments. The creators of the model report high rates of initial medication use, large reductions in ADHD symptoms and maintenance of effects over time. However, there are no randomized trials of this care pathway to date.

One limitation of these programs is that they were set in either university-based or other specialty BH settings that families had to be referred to or discover on their own. In addition, they employ trained BH staff, which may not be available outside of specialty settings. While some of the same principles have been applied in general pediatric settings as part of an integrated care model, there has been limited formal examination of their capacity to promote ADHD treatment in these settings. Silverstein *et al*[42] addressed this limitation by comparing the efficacy of an enhanced ADHD care management system *vs* a basic collaborative care intervention in urban primary care pediatric practices predominantly serving low-income families. All families referred by their primary care providers for an ADHD assessment were eligible with 40% of participating children found to have presentations consistent with ADHD. Nonclinical care managers in the enhanced arm were trained in an evidence-based parenting intervention and used preset MI scripts that focused on the benefits of medication usage. The two arms did not differ in levels of observed improvement over 12 mo with both groups showing reduced symptoms and improved social functioning over time. When analyses were limited only to the 40% of the sample with ADHD consistent presentations, significant differences in symptoms of ADHD and ODD as well as social skills were observed. Enhanced care was also associated with increased medication usage but had little impact on externally referred ADHD services[42]. Moreover, the specific impact of the use of MI was not able to be assessed apart from the larger treatment package.

Brinkman *et al*[139] completed a smaller study set in pediatric primary care designed to assess the capacity of a brief shared decision-making intervention to improve treatment uptake. The intervention offers psychoeducation about ADHD and its treatments while eliciting parental goals and treatment preferences. It was added to the initial treatment discussion with pediatrician for their child with ADHD (age range 6-10 years). This shared decision-making intervention was found to be feasible and well received by parents without increasing the duration of the visits. It improved parental knowledge of ADHD and increased initial interest in ADHD treatment. However, it had no impact on office contacts/visits or medication adherence over the next 90 d.

DISCUSSION

There are multiple evidence-based pharmacological and psychosocial treatments for ADHD, and greater service utilization is associated with improved acute and long-term outcomes[16,20]. However, long-term outcomes are suboptimal across countries and a major identified challenge to achieving optimal long-term outcome is sustained engagement with care. There are both structural and attitudinal barriers to care that serve as appreciable impediments to sustained engagement for many families of children with ADHD. Over the past two decades there has been increasing research identifying these barriers and developing interventions to overcome them. Many structural barriers are hard to modify such as geography and SES[12,19,20]. However, frequency of contact whether in person or remote improves treatment persistence[41,140]. Modifications to how and where pediatric BH care is administered have been effectively employed to increase contact and overcome other structural barriers. These interventions also broach attitudinal barriers by embedding care in less stigmatizing settings than specialty BH clinics. Engagement strategies have also been developed that directly address attitudinal barriers that can be applied wherever ADHD care occurs. These interventions include psychoeducation, MI or shared decision making. Other treatments, such as stepped care models, hold promise but their impact on engagement has not been systematically examined.

Integration of ADHD services into primary care

Integrated care for pediatric behavior problems have shown to be feasible and

effective across several studies. Integrating BH into primary care has enhanced outcomes, largely through increased service utilization of both medication and on-site counseling services[31,42,127]. Integration has been able to address both structural and attitudinal barriers by locating BH services in accessible primary care settings and building on families established relationships with their primary care providers[72]. Models employing full integration *vs* colocation of services have led to greater impact on the frequency of appointments for ADHD management[141]. Most models employ care managers who serve as the family's primary point of contact and guide them through the multiple aspects of care to reduce the burden of managing a chronic disease. Nurses and other primary care staff with little formal BH experience can be remotely trained and supported to accomplish these roles. Integrated models have also proved feasible and effective in populations with increased barriers to care[142]. However, integrated models require sizable effort and financial investment and are only beginning to become common occurrences in the United States[143]. Child Psychiatry access programs where primary care providers can access child psychiatrists when an acute need arises have become increasingly popular in the United States as they allow a single specialist to impact a broad geographic area. Many of these programs also offer care coordination services to families to help them connect to care. These programs have been effective at improving access to care and promoting evidence-based BH treatments for ADHD and other BH disorders in primary care[29,144].

Even when integration occurs, it is often not feasible to embed a full range of BH services into primary care. Therefore, referrals to external BH providers remain a common occurrence, and is a point in the care pathway where dropout often occurs [145]. Integrated models do not address the challenges of accessing referred care, which have proved particularly challenging to overcome[146]. Moreover, a sizable subset of families fails to engage integrated ADHD therapy services[42] in part because some stressed families do not inform PCCs about their child's struggles even when they view care as accessible[111]. Efforts to streamline and personalize the BH referral process that leverages the family's established relationship with their PCCs have been found to improve access to externally referred care[147].

Telehealth

For ADHD, increasing visits may promote engagement[140], but adding visits is challenging in primary care as stressed families are unlikely to come more frequently and long waits often preclude more frequent office visits with specialists. Rating scales and remote contact with families have proved as effective as office visits for improving ADHD outcomes[41,140], with less burden to staff and families than sole reliance on face-to-face interactions[148]. Therefore, collection of rating scales, communication through a patient portal or other forms of asynchronous or synchronous remote contact can be used to build engagement, especially in areas with long travel distances to care.

Telehealth has been recommended as an effective means to increase access and improve engagement for pediatric BH services[149,150]. In children with ADHD, meaningful changes in functioning have been captured through telehealth interventions[125-127], and several evidence-based psychosocial interventions for pediatric behavioral problem have been adapted for telehealth application[151]. There is an emerging evidence base to support both direct patient care and peer-to-peer consultation models using telehealth[29,126,127]. These tele-methods are effective for underserved families and have found to be palatable across race and ethnicity[126,127]. The effectiveness of these techniques for the chronic care of ADHD has not been studied as published studies have not extended beyond 6 mo[152].

Tele methods have become increasingly common during the coronavirus pandemic [153-155] given the multiple barriers to face-to-face contact. Treatment guidelines for ADHD telecare during the pandemic are being developed[154,155] and rules requiring a face-to-face visit for prescription of controlled substances medications have been loosed during the pandemic in the United States. European ADHD Guidelines report it is reasonable to start ADHD medications during the pandemic for patients who did not have a baseline, face-to face cardiovascular assessment if they meet following 3 criteria: (1) No personal history of cardiac symptoms; (2) No family history of early (< 40 years) sudden death in a first degree relative; and (3) Patient must have baseline measurement of blood pressure and heart rate by a family member or another person remotely on three separate occasions. If the first two conditions are not satisfied, a referral to a pediatric cardiologist should be made before starting the medication for the ADHD[155].

Assessing and enhancing motivation for ADHD care

Chronic care models assessing functioning and motivation starting when care begins are recommended[156]. Failure to synchronize treatment intensity for a chronic disorder like ADHD to the motivational state of the family can lead to feelings of defeat and disengagement[157]. Families of ADHD youth have higher rates of parental ADHD, depression, divorce and exposure to adverse childhood experiences, which all impair motivation[20,158]. Initial evaluations should assess for a wide range of psychosocial stressors impacting the patient and the family as well as assessing parent-child and family relationships[64]. Initially, stress may promote change as it can lead to treatment seeking efforts[19]. However, chronically worsening stress impedes change, as stressed families are more apt to decide the current state is unmodifiable, especially when there are financial barriers to care[38]. Waiting too long to assess motivation risks families dropping out of care[84]. The combination of waning motivation and reports of increasing impairment or family strain indicate increased risk for dropout.

The success of any initial treatment is always contingent on the family's motivation to make a change in their child's behavior, whether this is through giving medication or attending a counseling visit. According to the transtheoretical model, change is a process, progressing from recognizing an undesirable behavior, to contemplating change, to intending to act, to modifying the behavior and then to maintaining the desired state[130,159]. Goal achievement is most likely when progression is sequential and the motivational stage is used to inform treatment decisions. Therefore, efforts to improve motivation should be a fluid process tailored to the status of the patient and family at the current time. Current ADHD guidelines recommend repeatedly measuring motivation and using results to tailor an individualized care plan[3,5].

Cunningham has applied the transtheoretical model of change to ADHD care[160]. Contacting the PCCs is the most common first step in the ADHD care pathway[119]. Parents presenting to a care provider with concerns about their child's ADHD are likely at the preparation stage[159] as they have achieved an awareness of their child's struggles and have a goal to improve them. However, adolescents are often not at the same stage as their parents, and direct assessment of their motivation for care is critical. To move towards action, a palatable treatment option that parents and adolescents feel they can access and successfully implement to achieve their goal must be identified[161]. Psychoeducation may be help for more receptive families towards starting treatment[113] but simply providing information about treatment options is unlikely to move many parents and teens from preparation to action to maintenance of changes[34,113,114]. Some families presenting for assessment are not ready for active treatment even if their child is appreciably impaired. For example, external forces such as schools may drive people into the office who are only in the contemplation stage. For them, it may be critical to address motivation for care prior to directly promoting treatment.

MI is widely used to help patients down to age 12 to clarify goals, explore the benefits and risks of engaging in treatment[130,162,163], address stigma and other attitudinal barriers and promote self-efficacy to benefit from treatment seeking efforts [132]. Simple single item motivation rulers can be employed to measure each of these core aspects of motivation (readiness and desire to change, self-efficacy to implement change, treatment preferences and overcoming perceive barriers) as they have been found to predict health behaviors in adults[164] and adolescents[165].

Initial change behaviors can be nurtured by expressing an interest in family's views about the sources of their child's problems while rolling with their resistance to change. Minimizing their concerns or attempting to solve problems for them may reduce self-efficacy and threaten autonomy. Empathetically providing patients with objective feedback on differences between current *vs* desired functioning can be used to generate change talk to enhance readiness and desire to change. Recognizing areas where the child is doing well and instances where parents have successfully achieved past goals for their child promotes self-efficacy to move forward with identified changes. Once parents have identified a specific goal that they feel motivated to and capable of achieving, they may be most receptive to discussing specific treatments. Shared decision-making can then be used to identify a treatment that matches their goals, while also crafting realistic treatment expectations to increase the chances that families will initiate new services for ADHD. To engage adolescents, it is essential that treatment centers around their goals *vs* parental or provider goals to create engagement[139]. Clinicians may need to aide parents and teens in identifying a mutually acceptable treatment goal. Parental input on ways to incentivize the adolescent working towards their goal (making curfews or screen time contingent on making visible effort to achieve a goal) can be elicited. To foster sustained engagement,

providers should empathically affirm treatment seeking behaviors by parents and adolescents, aide in finding supports and reinforcers to sustain ongoing change behavior and offer to help them plan to overcome identified barriers[159,166].

These techniques of MI have been integrated with high fidelity into several counseling interventions for ADHD[102,123,135]. They have also been used to increase medication adherence in general medical and specialty settings[42,136,137]. Modifying the format of existing counseling interventions to increase interest (*e.g.*, Fabiano's COACHES for fathers) or supplementing the content to address specific barriers for populations with multiple impediments to engagement (Chacko's STEPP for single mothers or Sibley's STAND for adolescents with academic struggles) have also been employed. Modifying content could potentially reduce efficacy for primary outcomes or increase dropout if new content is added; however, controlled results support that these adaptations increase attendance, participation and satisfaction with some producing better outcomes than the unmodified interventions[108,134].

Other modifiable factors for promoting engagement

Medication issues: Parents' most frequently cited reasons for discontinuing ADHD medication is lack of efficacy or intolerable adverse effects. Health care providers should closely monitor patients during the dose optimization phase using structured measures of efficacy and tolerability. Once dose is optimized, monitoring should assess functioning, adherence, tolerability and ongoing need for medication. For adolescents, it is also important to directly assess their perceptions of the need for medication and ensure that medication addresses a goal that is relevant to them. Reducing the number of doses per day by switching to long-acting preparations has been found to increase compliance with medications for ADHD[25,26,28,167]. Formulation alterations, such as liquids, patches or chew tabs can also be an option, for children either who have difficulties in swallowing pills.

Involvement of all caregivers: Caretakers may have differing views on the severity and cause of the child's behavioral struggles. They may also be at different stages of change in regards to treatment seeking efforts, especially when they reside apart[3,168]. Therefore, efforts should be made to contact all custodial caretakers to assess their personal views. It has been found identifying parental attributions for the child's problem behaviors that emphasize the capacity of the parent to promote positive change has been found to increase engagement for fathers not residing full time with the child[71]. Strengthening support networks enhances service initiation and persistence with care, while fathers' participation in care improves maintenance of treatment effects[169]. Therefore, engaging all caretakers can be a means to increase the amount and the impact of utilized services. Telehealth may be a particularly useful tool to engage fathers, as they are less likely to present for office-based care[20]. It can also be used to separately engage caretakers prone to disagree with each other. Reducing conflict between parents may be another means to engage fathers as perceived criticism from the mother is a major risk for their dropout from treatment [104].

Stepped care*:* The appreciable commitments required of parents for intensive counseling interventions may be one reason why stressed families receive less benefit from these programs[170]. Stepped care reduces burden without sacrificing impact, as low intensity treatments are initiated for all, followed by incrementally more intensive services if impairment persists. Combining stepped care with tailoring approaches to individualize subsequent care further minimizes burden and is recommended for treating childhood behavior problems[152].

There is evidence of efficacy of stepped care for ADHD in controlled settings, with the sequence of behavior therapy followed by medication leading to the greatest enhancements in functioning at a lower cost than starting with medication[62,77]. Stepped care models for ADHD have not been examined outside the confines of research studies. However, there is evidence that medication usage reduces parental motivation for psychosocial services both in controlled and naturalistic settings[10,77]. For multiply stressed families, lower intensity counseling programs have been found to be less costly and not inferior in efficacy to more intensive programs such as Parent Child Interaction[152]. They may be the preferred initial intervention especially for families with multiple barriers to high intensity care.

Limitation

Most studies assessing barriers to care are drawn from Western Europe and the United States while the vast majority of the trials of interventions designed to promote

engagement were run in the United States. Integrated models for pediatric BH care have not been well studied outside of the United States, possibly in part due to national policies regarding the payment and provision of BH care that are separate from the those for the rest of medicine. Cultural perceptions of ADHD and health care policy varies widely across the globe, limiting the generalizability of these findings. While behavioral parenting interventions are efficacious in countries beyond their origin[171], the impact of engagement barriers and interventions for them could variably appreciably given the impact of culture on perceptions of pediatric BH[43]. It was encouraging to see that several studies recruited racially and ethnically diverse families[42,123] with a focus on populations that are less likely to access BH care[102, 134]. Furthermore, there are only a few RCT specifically designed to measure engagement and even less that track engagement for more than 6 mo. Additionally, most interventions were multi-pronged, so it is hard to determine the impact of any single engagement technique. The heterogeneity of the interventions and assessment methods used to measure and promote engagement further inhibited the ability to draw conclusions from the collective literature base. Only a limited number of studies have examined how to improve uptake of externally referred services, which remain a common form of treatment[146].

CONCLUSION

Despite a number of evidence-based treatments, long-term outcomes for youth with ADHD remain suboptimal. ADHD care often ends quickly even when high levels of impairment persist. Families face a variety of structural and attitudinal barriers to engagement, ranging from cost and access to stigma and low self-efficacy to successfully implement change. Integration of BH into general medical settings and telehealth have been found in controlled studies to increase access by reducing both structural and attitudinal barriers. Adding MI, shared decision-making and other engagement interventions to evidence-based ADHD treatments reduces altitudinal barriers that translates to improved participation and satisfaction with care while enhancing outcomes. However, improving uptake of externally referred BH services remains a challenge and little is known about how to enhance long-term engagement with ADHD services even though a chronic care model for ADHD is recommended.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1228-1238

DOI: 10.5498/wjp.v11.i12.1228

ISSN 2220-3206 (online)

MINIREVIEWS

Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise?

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Author contributions: Majumder P, Barman R, and Doifode T performed the literature search with author Kablinger A as a consultant; Majumder P, Barman R, and Doifode T wrote the initial draft; Kablinger A provided feedback and elaboration on the manuscript; all authors approved the final version.

Conflict-of-interest statement: We do not have any conflict of interest.

Country/Territory of origin: United States

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an

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Abstract

Antipsychotic agents are used for various indications in the treatment of psychiatric disorders. Despite their proven roles in multiple conditions, the treatment-emergent side effects of antipsychotic medications, such as metabolic side effects, are often the limiting factor for their long-term and short-term uses. Moreover, antipsychotic medications are often criticized for being less effective in treating different disabling symptoms such as negative symptoms of schizophrenia. As a result, the search for safer and more efficacious antipsychotic agents is ongoing. Newer antipsychotic agents are gaining attention related to emerging efficacy and tolerability data in treating neuropsychiatric conditions. In this review, we attempt to appraise the scientific data on psychopharmacology, safety profile, and efficacy of the newer additions to the list of second-generation antipsychotics, namely brexpiprazole, cariprazine, and lumateperone. We conducted a selective review utilizing PubMed, clinicaltrials.gov, and Cochrane databases to gather appropriate publications, keeping broad inclusion criteria. There were no restrictions on the age of the study population or the year of publication. We also cross-referenced articles and references to capture all existing studies. Our review of the current literature indicates that all three antipsychotic agents appear to be promising based on their short-term studies, while long-term studies remain limited. There is also a need for a head to head comparison between the newer antipsychotics with the other antipsychotic agents to ascertain if the newer agents are any better than the others.

Key Words: Antipsychotic agent; Brexpiprazole; Cariprazine; Lumateperone; Psychopharmacology; Schizophrenia

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Received: February 20, 2021
Peer-review started: February 20, 2021
First decision: July 15, 2021
Revised: July 28, 2021
Accepted: October 27, 2021
Article in press: October 27, 2021
Published online: December 19, 2021

P-Reviewer: Hosak L
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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Core Tip: In this review article we attempted to appraise the scientific literature on three newer antipsychotics such as brexpiprazole, cariprazine and lumateperone and presented their safety and efficacy data. Our aim was to investigate the status of these antipsychotic agents in treating various psychiatric disorders.

Citation: Barman R, Majumder P, Doifode T, Kablinger A. Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise? *World J Psychiatr* 2021; 11(12): 1228-1238
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1228.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1228

INTRODUCTION

Antipsychotics have revolutionized the treatment of psychiatric disorders in the last few decades[1]. Despite advances in psychopharmacology, the quest for more effective and safer antipsychotic medications is not yet over. Schizophrenia remains one of the most chronic, debilitating psychiatric disorders whose optimal treatment approach is still a matter of research. In a global burden of disease study involving more than 30000 respondents from four European countries, schizophrenia was found to have the highest functional burden across hundreds of physical and mental health issues[2]. Second-generation antipsychotics (SGAs) are commonly used to treat schizophrenia and other conditions, including bipolar disorder[3-5]. Despite their proven efficacy, existing antipsychotic medications are limited by treatment-emergent side effects and their ability to address a limited collection of symptoms of schizophrenia such as delusions, hallucinations, disorganized thoughts, and bizarre behavior[6]. The lack of efficacy of medications to treat negative symptoms of schizophrenia, poor quality of life, and medication non-adherence remain a challenge[7,8]. Clozapine, which was introduced in 1971, remains the most efficacious antipsychotic medication despite potentially dangerous side effects[9]. This review aims to appraise the scientific data on psychopharmacology, safety profile, and efficacy of the newer additions to the list of SGAs, including brexpiprazole, cariprazine, and lumateperone.

LITERATURE SEARCH

We conducted a selective review utilizing PubMed, clinicaltrials.gov, and Cochrane databases to gather appropriate publications. The search was carried out between December 2020 to January 2021, keeping broad inclusion criteria to ensure the incorporation of relevant articles. There were no restrictions on the age of the study population or the year of publication. The authors cross-referenced articles and references to capture all existing studies. Authors PM, RB, and TD performed the literature search with author AK as a consultant. PM, RB, and TD wrote the initial draft and AK provided feedback and elaboration on the manuscript. All authors approved the final version.

BREXPIPRAZOLE

Brexpiprazole, a novel serotonin-dopamine activity modulator, a partial agonist of the dopamine D2 receptors and is structurally similar to its predecessor, aripiprazole. Brexpiprazole is also a partial agonist at serotonin 1A (5-HT1A) receptors and a potent antagonist at 5-HT2A, α1B, and α2C adrenergic receptors[10]. This newer antipsychotic has less intrinsic agonist activity at the D2 receptor compared to aripiprazole and, as a result, may be less activating (as manifested by agitation and restlessness) than aripiprazole[11]. Antagonism of 5-HT2A and α1B receptors and agonism of 5-HT1A receptors decrease side effects related to D2 receptor blockade in the striatum including akathisia and other extrapyramidal side effects (EPS) due to an increased

release of dopamine downstream[11,12]. Compared to aripiprazole, brexpiprazole has increased potency at these three receptors, namely, 5-HT2A, 5-HT1A, and α1B leading to fewer potential treatment-emergent movement effects. Brexpiprazole also has lower antihistamine activity at the H1 receptor, and as a result, may be associated with less sedation and weight gain than aripiprazole[11]. Brexpiprazole has no apparent anticholinergic side-effects given its minimal activity and affinity for the muscarinic acetylcholine receptors[12]. CYP3A4 and CYP2D6 primarily metabolize brexpiprazole to DM-3411, an inactive metabolite; has about 95% bioavailability after oral administration, and achieves peak plasma concentration 4 h after administration, and a steady-state concentration is reached within 10-12 d of daily administration[13].

Safety and efficacy data of brexpiprazole in schizophrenia research

On July 10, 2015, the United States Food and Drug Administration (FDA) approved brexpiprazole for the maintenance treatment of schizophrenia and as an adjunct treatment to antidepressants for the treatment of major depressive disorder (MDD) in adults[14]. However, brexpiprazole continues to be examined in clinical trials for possible use in attention deficit hyperactivity disorder, autism, conduct disorder, oppositional defiant disorder, Bipolar disorder, and agitation in Alzheimer's disease [15,16].

VECTOR[17] and BEACON[18] trials are the two major studies establishing the efficacy of brexpiprazole in schizophrenia treatment. These two, 6-wk, phase 3, randomized, placebo-controlled clinical trials used fixed doses of brexpiprazole *vs* placebo in patients with acute schizophrenia. Brexpiprazole demonstrated statistically significant improvement in the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions-Severity (CGI-S) in both studies. In the VECTOR trial, Correll *et al*[19] demonstrated a statistically significant reduction in PANSS scores with both 2 and 4 mg brexpiprazole compared to placebo[19]. On the other hand, in the BEACON trial, Kane *et al*[20] found a statistically significant decrease in PANSS scores with the 4 mg brexpiprazole dose group only, not with 1 or 2 mg doses, compared to placebo[20]. However, both VECTOR and BEACON trials lacked active comparators and were short term trials. Few studies have established the long-term efficacy of brexpiprazole as maintenance therapy for schizophrenia. In a phase 3, randomized, double-blind, placebo-controlled trial, Fleischhacker *et al*[21] demonstrated that patients taking brexpiprazole had significantly longer time to impending relapse and a lower rate of relapse (13.5% *vs* 38.5%) as compared to placebo[21,22]. ZENITH trial [23], a 52-wk, open-label brexpiprazole study, reported that the PANSS total score improved on average by 12.2 points in patients receiving brexpiprazole. There was an improvement in mean CGI-S score of 0.6 and Personal and Social Performance scale total score of 7.7 points in patients taking brexpiprazole[24]. A recent randomized, double-blind, functional magnetic resonance imaging (fMRI) study[25] evaluating the effects of brexpiprazole on brain regions that control impulsive behavior in patients with stable schizophrenia reported that this medication decreased right ventrolateral prefrontal cortex (VLPFC) activation and decreased stop-signal reaction time (SSRT). The stop-signal task was a task associated with inhibition/control of impulsivity. Thus, this study concluded that brexpiprazole might be exerting benefits on inhibition-related brain activation and behavior in patients with schizophrenia[26]. Brexpiprazole was well-tolerated in schizophrenia trials with akathisia, headache, somnolence, tremor, weight gain as commonly reported side effects[13].

Safety and efficacy data of brexpiprazole in MDD research

PYXIS[27] and POLARIS[28] phase 3 trials led to the FDA approval of brexpiprazole as an adjunctive treatment for MDD. Both of these studies were six weeks, randomized, double-blind, and placebo-controlled, and evaluated the efficacy of brexpiprazole as an adjunctive treatment in MDD by comparing changes in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score. The participants were adult patients with MDD with an inadequate response to 1-3 previous antidepressant trials. Both studies had an 8-wk single-blind prospective treatment phase where subjects received a standard antidepressant; those with inadequate responses were included in the study. In the POLARIS trial, 3 mg brexpiprazole demonstrated a statistically significant improvement in MADRS score as compared to placebo. However, brexpiprazole 1 mg did not reach statistical significance[29]. Similarly, the PYXIS trial, which used 2 mg brexpiprazole dosing, also reported a reduced mean MADRS total score compared to placebo corroborating its efficacy as an adjuvant treatment in MDD[30].

Data from short- and long-term trials of brexpiprazole as a treatment adjunct in MDD reported minimal changes in prolactin levels, low rates of post-baseline prolactin elevation, low rates of prolactin-related side effects, and a moderate improvement in

sexual functioning[31]. Akathisia, headache, somnolence, tremor, and weight gain were reported as common side effects[13].

CARIPRAZINE

Cariprazine is a SGA approved by the United States FDA in 2015 for the maintenance treatment of schizophrenia[32]. While most atypical antipsychotics are D2 antagonists, cariprazine is a dopamine D3/D2 receptor partial agonist with a 10-fold higher affinity for D3 receptors than D2 receptors[33,34]. Cariprazine differs from two other dopamine receptor partial agonists, aripiprazole and brexpiprazole, by its distinct receptor-binding characteristics not only at dopamine D2/D3 receptors but also at serotonin 5HT1A, 5HT2B, 5HT2A, 5HT2C, and histamine H1 receptors[35]. Structurally, cariprazine is an antagonist at the dopamine D3 receptor but functionally acts as a partial agonist with 70% intrinsic agonism[34]. Dopamine D3 receptors in the prefrontal cortex regulate cognition, mood, and negative symptoms and are also distributed in other brain regions, including the nucleus accumbens that controls reward and motivation. Cariprazine, as an antagonist of the dopamine D3 autoreceptors, is hypothesized to play a role in motivation, depression, and reward by increasing dopamine release in the prefrontal cortex[36].

The pharmacokinetic characteristics of cariprazine are also distinct from other antipsychotics. Cariprazine is highly plasma protein bound, time to peak concentration is 3-6 h[37] and it is primarily metabolized by CYP 3A4, and by CYP 2D6, to a lesser extent. It has two major active metabolites, desmethyl cariprazine, and didesmethyl cariprazine. Didesmethyl-cariprazine (DDCAR) has a long half-life of 1-3 wk[38]. A longer half-life might protect against the rapid onset of relapse following non-adherence in patients with schizophrenia.

Safety and efficacy data of cariprazine in schizophrenia research

Among the four major randomized, placebo-controlled pivotal trials, one trial of cariprazine in the treatment of schizophrenia failed as the placebo response was much higher than the cariprazine group[39]. In the other three trials, all tested cariprazine dosages of 1.5, 3, 4.5, 6, 3-6, and 6-9 mg/d, were superior to placebo in reducing the PANSS and CGI-S scores[40-42]. A significant improvement in the hostility item of the PANSS was observed in these three studies. In two metanalyses, both higher and lower dosages of cariprazine demonstrated superior efficacy as compared to placebo in acute schizophrenia[43,44].

Safety data collected from these four trials reported a lower discontinuation rate in the patients who received cariprazine 1.5-6 mg/d compared to patients on placebo [35]. Pooled data on adverse effects noted a higher likelihood of weight gain, hypertension, akathisia, and EPS that led the FDA to recommend the lower dose range of 1.5 to 6 mg/d in schizophrenia[45,46]. In the pooled data, mean changes in metabolic parameters and hypotension were no different from the placebo group; there were also no differences in syncope, prolactin level, or Qtc > 500 ms[46,47]. As *per* the product label, the most common side effects are EPS and akathisia[45]. In a study among 586 patients with schizophrenia[48], the most common adverse effect was akathisia (16%), followed by headache, insomnia, and weight gain. However, the discontinuation rate from akathisia was < 1% in comparison to 12.5 % from all other adverse events. Among the D2 partial agonist antipsychotics, the risk of weight gain and somnolence is much lower with cariprazine, but akathisia is higher than with aripiprazole and brexpiprazole[47]. In placebo-controlled studies, observed relapse rates were much higher in the placebo group than the patients on cariprazine 47.5% *vs* 24.8%[49]. Because of longer half-life, relapse at 4 wk following discontinuation of cariprazine was 2-7 times lower than in other relapse prevention studies[50].

Safety and efficacy data of cariprazine in mood & anxiety disorders research

Cariprazine is also approved in the United States for mania and mixed episodes related to bipolar mood disorder type I in adults[51]. In bipolar mania, more cariprazine treated patients had improved CGI-S scores than patients on placebo; that is, more cariprazine-treated patients shifted from the severely ill to the mildly ill or better category as compared to the placebo-treated patients (55% *vs* 36%, odds ratio = 2.1)[51]. Post hoc analyses of three randomized, double-blind, placebo-controlled clinical studies showed that a significantly higher proportion of patients with cariprazine achieved response and remission in bipolar mania on all evaluated measures when compared with the placebo-treated group[52]. Most importantly,

improvement in manic symptoms did not precipitate depressive symptoms. Subsequent research on the role of cariprazine in bipolar I depression and MDD are being studied.

In animal studies, cariprazine has demonstrated antidepressant-like activity and has reduced anhedonia-like behavior[53], comparable to aripiprazole and the tricyclic antidepressant imipramine[54]. In the same study by Duric *et al*[54], the anxiolytic-like action of cariprazine has also been elicited in mice. Theoretically, cariprazine may improve depressive symptoms because of its unique D3 preferring dopamine D3/D2 receptor partial agonism along with serotonin 5HT1A receptor partial agonism. However, in a randomized, double-blind, placebo-controlled phase 3 trial, cariprazine did not show significant benefit as an augmenting agent in MDD, though it was well-tolerated with no significant differences in side effects compared to placebo[55].

On the contrary, in a study by Earley *et al*[56], cariprazine at 1.5-3 mg/d was safe and effective in reducing the depressive symptoms in bipolar I depression[56]. In a recent placebo-controlled study, cariprazine 1.5 mg/d significantly reduced depressive symptoms but not cariprazine 3 mg/d[57]. Clearly, the efficacy of cariprazine in bipolar I depression is not yet fully established.

Additional studies of cariprazine

In a case series described by Sanders and Miller[58], three cases of type I bipolar mood disorder with co-morbid substance abuse elicited an abrupt decrease in craving and use of the substances concomitant with improved mood symptoms after initiating cariprazine with their existing medication regimen. Findings in animal studies demonstrate that cariprazine improves cognition, improves pro-social behavior, and decreases the rewarding effect of cocaine[59]. Interestingly, cariprazine can resensitize resistant cancer cells to mitoxantrone by modulating ABCG2 (breast cancer resistance protein) and *via* several other distinct mechanisms[60].

LUMATEPERONE

Lumateperone[7], received United States FDA approval to treat schizophrenia in adults in December 2019[61]. Lumateperone possesses unique pharmacologic actions on the serotonin, glutamine, and dopamine systems. It is a presynaptic partial agonist and postsynaptic antagonist at D_2 receptors, an antagonist at serotonin 5-HT_{2A} receptors, and a glutamate modulator[7,8,62]. The presynaptic partial agonism and postsynaptic antagonism at dopamine D_2 receptors allow a lowered presynaptic release of dopamine and postsynaptic blockade of dopamine, leading to a more efficient reduction of dopaminergic signaling than other antipsychotic medications [63]. At the same time, it has negligible binding potential to other receptors such as histaminic or muscarinic receptors, which are associated with sedation, cognitive and metabolic side-effects[63]. One of the critical components of lumateperone is the 60-fold separation between its affinity for 5-HT_{2A} receptors and D_2 receptors. At a lower dose, lumateperone antagonizes the 5-HT2A receptor and promotes sleep and reduces aggression, but at a higher dose, antipsychotic and antidepressant effects emerge[63,64]. It also indirectly modulates the glutamatergic phosphoprotein associated with D1-dependent augmentation of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) activity *via* the mammalian target of the rapamycin (mTOR) pathway, which could contribute to a potent and rapid antidepressant action[65]. Additional actions such as serotonin transporter inhibition and stimulation of phosphorylation of glutamatergic NMDA $GluN_{2B}$ receptors[8] are unique to lumateperone. The steady-state concentration is reached in approximately five days and is metabolized by several enzymes, including but not limited to uridine 5'- diphospho-glucuronosyltransferases (UDP-glucuronosyltransferase, UGT) 1A1, 1A4, and 2B15, aldoketoreductase (AKR)1C1, 1B10, and 1C4, and cytochrome P450 (CYP) 3A4, 2C8, and 1A2[66]. The half-life of lumateperone and its metabolites ranges from 13 to 21 h which allows a once a day dosing regimen[8].

Safety and efficacy data of lumateperone in schizophrenia research

Three industry-sponsored placebo-controlled trials among patients with an acute exacerbation of schizophrenia have investigated the role of lumateperone in the treatment of schizophrenia[67-70]. Correll *et al*[71], in a four-week-long, three-armed placebo-controlled, randomized phase 3 clinical trial[71], involving 450 patients aged 18-60, with acute exacerbation of schizophrenia, demonstrated that 42 mg of lumateperone (equivalent to 60 mg of lumateperone tosylate), brought significant improve-

ment as compared to placebo from baseline to day 28 on the PANSS total score and the CGI-S[71]. There was no statistically significant difference between 28 mg of lumateperone (equivalent to 40 mg of lumateperone tosylate), as compared to placebo. A previous phase 2 multi-site randomized, double-blind, placebo-controlled, and active-controlled trial (risperidone) involving 335 acutely psychotic patients with schizophrenia also demonstrated antipsychotic efficacy at 42 mg (equivalent to 60 mg of lumateperone tosylate), but not at the 84 mg dose (equivalent to 120 mg of lumateperone tosylate)[72]. A subgroup analysis revealed that the forty-two mg also significantly reduced the total PANSS and the Calgary Depression Scale for Schizophrenia (CDSS) score with an effect size much larger than risperidone (effects sizes for PANSS and CDSS approximated 1 for lumateperone, and 0.60 and -0.48, respectively for risperidone). The improvement in negative symptoms with lumateperone 42 mg did not reach statistical significance. The authors concluded that the lack of a significant difference was due to relatively low negative symptoms at baseline[72]. In another phase 3 randomized clinical trial[73], involving 696 subjects, 60 mg, and 20 mg lumateperone tosylate were compared with risperidone 4 mg and placebo for six weeks, but lumateperone (at either dose) was not significantly different from the placebo on the primary endpoint in the intent-to-treat population[74]. Such results may be related to an unusually high placebo response rate at specific sites, which affected the overall results. In a position emission tomography study[75] in patients with schizophrenia, the mean peak dorsal striatal D2 receptor blockade was 39% attained after an hour of taking 60 mg lumateperone tosylate. Higher D2 receptor occupancy is associated with a higher risk of EPS and hyperprolactinemia, indicating lumateperone may be associated with less risk of EPS and hyperprolactinemia[76].

All studies indicate a favorable side-effect profile of lumateperone. Lumateperone was also favorable to risperidone in terms of safety and tolerability, including a lower risk of hyperprolactinemia, hyperglycemia, hyperlipidemia, and weight gain. The most commonly reported adverse effects with lumateperone are mild sedation and somnolence. The most common side effect reported by Correll *et al*[71] was sedation (9.3%-12.7%), followed by fatigue (4.7%-5.3%), and constipation (4%-6.7%) among lumateperone- treated patients. In the same study, two patients discontinued treatment due to severe, treatment-emergent adverse- effects: One developed orthostatic hypotension and the other one developed convulsions with preexisting risk factors. There was no increase in suicidal ideation or behavioral or EPS[71]. In the other trial, by Lieberman *et al*[72], no severe adverse reaction occurred in the lumateperone group[72]. In the same study, two patients discontinued treatment in the lumateperone group- one for dryness of mouth and another for worsening schizophrenia whereas, three patients stopped treatment in the risperidone group due to akathisia and increased creatine phosphokinase level; 17% developed somnolence. There was no difference in the median weight gain between lumateperone and placebo groups; interestingly, the median weight gain was less than the patients on risperidone experienced (2.5 kg *vs* 1 kg), and no EPS were reported[72]. In an open-label safety switching trial, 301 patients with stable symptoms of schizophrenia were switched from previous antipsychotic medication to a daily dose of 60 mg lumateperone tosylate for six weeks and then switched back to the previous or another antipsychotic and reassessed after two additional weeks[77]. The study demonstrated a statistically significant improvement in total cholesterol, low-density lipoprotein cholesterol, body weight, and prolactin with switching to lumateperone. The progress was reversed as the treatment was changed back to the previous antipsychotic medication[77]. The most commonly reported side effects were mild to moderate and comprised of somnolence (6.6%), headache (5.3%), and dry mouth (5.3%), EPA (1.0%)[77]. Part 2 of the open-label study[78], is currently evaluating the safety and efficacy of switching to 60 mg lumateperone from the previous antipsychotic medication. In another study, one hundred seven patients experienced a mean reduction of 1.82 kg weight by day 175 and 3.16 kg by day 350. Almost 24% had at least 7% weight loss. The most common side effects were somnolence (20%), dryness of the mouth (7%), headache (7%), diarrhea (7%), and EPS (0.8%). The rate of somnolence decreased with night administration[79].

Summary of comparisons between newer FDA approved antipsychotics and the other SGAs

Although there is a lack of head-to-head comparisons among the newer antipsychotic medications, there is some evidence showing possible differences. In three 26-wk randomized clinical trials in Europe, higher efficacy of cariprazine over risperidone for negative symptoms has been established[40,80,81]. In a recent retrospective chart

Table 1 Characteristics and indications of brexpiprazole, cariprazine, and lumateperone

Name	Characteristics	Dose	Common adverse reactions	FDA indications
Brexpiprazole	Partial agonist of dopamine D2 receptor, a partial agonist of serotonin 1A (5-HT1A) receptors, and a potent antagonist at 5-HT2A, α1B, and α2C adrenergic receptors	2-4 mg/d for schizophrenia; 2 mg/d for MDD	Akathisia, headache, somnolence, tremor, and weight gain	Maintenance treatment of schizophrenia Adjunctive treatment for major depressive disorder in adults
Cariprazine	Dopamine D3/D2 receptor partial agonist with 10-fold higher affinity for D3 receptors than D2 receptors, antagonism at serotonin $5HT_{2A}$, $5HT_{2B}$ with moderate to high binding affinity	1.5 mg/d-6 mg/d for schizophrenia; 3-6 mg/d for bipolar mania	Akathisia, EPS, headaches, weight gain, headache, insomnia, and extrapyramidal side effects	Maintenance treatment of schizophrenia. Mania and mixed episodes related to bipolar mood disorder type I in adults
Lumateperone	Presynaptic partial agonist and postsynaptic antagonist at D_2 receptors, an antagonist at serotonin 5-HT_{2A} receptors, and a glutamate modulator	42 mg for schizophrenia	Sedation, somnolence, headache, dryness of mouth, extrapyramidal side effects	Schizophrenia in adults

FDA: Food and Drug Administration; MDD: Major depressive disorder; EPS: Extrapyramidal side effects.

review, the metabolic parameters of patients treated with brexpiprazole, lurasidone, asenapine, cariprazine, or iloperidone were assessed at six weeks, 12 wk, and up to 12 mo. Olanzapine was used as a comparator. Although all the newer antipsychotics had significantly favorable metabolic characteristics compared to olanzapine, the risk of weight gain and increased body mass index was more with brexpiprazole and iloperidone among the newer antipsychotics. In contrast, a minimal increase in weight was reported with cariprazine and asenapine[64]. Among the three dopamine partial agonists (aripiprazole, brexpiprazole, and cariprazine), patients on aripiprazole had the most significant reduction of PANSS scores in schizophrenia, cariprazine had the most potent effects on Young Mania Rating Scale scores in mania, and brexpiprazole significantly reduced the MADRS score as an adjunctive treatment of MDD[35]. However, a recent systematic review and network meta-analysis concluded that there was no difference in the safety and efficacy between aripiprazole and brexpiprazole in the treatment of schizophrenia[82].

CONCLUSION

Brexpiprazole, cariprazine, and lumateperone have demonstrated efficacy in treating schizophrenia in the short term. Longer-term studies are limited in number. Based on short-term studies, all three newer antipsychotics appear to be promising, specifically due to fewer metabolic side effects and possible efficacy on negative symptoms in schizophrenia (Table 1). Further research focusing on comparative effectiveness will aid in identifying whether brexpiprazole, cariprazine, and lumateperone are truly better than their precursors. Future studies should compare the safety and efficacy of these newer antipsychotics with older antipsychotic medications to provide patterns or predictors with respect to efficacy in particular patient groups.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1239-1246

DOI: 10.5498/wjp.v11.i12.1239

ISSN 2220-3206 (online)

MINIREVIEWS

E-technology social support programs for autistic children: Can they work?

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Author contributions: Wall NG designed the paper outline and performed the majority of the writing; Smith O performed writing and prepared the figure; Campbell LE, Loughland C, Wallis M and Henskens F provided input in writing the paper; Schall U provided input, designed the figure, and coordinated the writing of the paper.

Conflict-of-interest statement: The authors declare no conflict of interest.

Supported by Hunter Medical Research Institute (Happy, Healthy Kids), No. G1801008; and an Australian Government Research Training Program Fee Offset and Scholarship.

Country/Territory of origin: Australia

Specialty type: Psychiatry

Provenance and peer review:

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Abstract

Autism is a neurodevelopmental condition with associated difficulties that present differently across individuals. One such difficulty is recognizing basic and complex facial expressions. Research has previously found that there are many evidence-based support programs available for building non-verbal communication skills. These programs are frequently administered with a therapist or in a group setting, making them inflexible in nature. Programs hosted on e-technology are becoming increasingly popular, with many parents supportive of them. Applications (apps) that are hosted on technology such as iPads or mobile phones allow users to engage in building skills in real-time social settings and own what they are learning. These technologies are frequently used by autistic children, with apps typically focusing on identifying facial features. Yet at this current time, there are mixed reviews of how to design such programs and what their theoretical backing is, with many studies using a mix of observation and psychological assessments as outcome measures. Eye-tracking and electroencephalography are established methodologies that measure neural processing and gaze behaviors while viewing faces. To better support the field moving forward, objective measures such as these are a way to measure outcomes of apps that are designed for helping children on the spectrum build skills in understanding facial expressions.

Key Words: Autism; Facial expression recognition; Technology; Eye-tracking; Electroen-

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: February 26, 2021
Peer-review started: February 26, 2021
First decision: July 15, 2021
Revised: August 4, 2021
Accepted: November 1, 2021
Article in press: November 1, 2021
Published online: December 19, 2021

P-Reviewer: Zheng HJ
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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Core Tip: Social support programs hosted on interactive technologies are becoming increasingly popular in the field of autism research. There are varied methods by which researchers determine the effectiveness of these programs. The review aims to address the current field by providing recommendations for assessing evidence-based tablet applications that support social skill development.

Citation: Wall NG, Smith O, Campbell LE, Loughland C, Wallis M, Henskens F, Schall U. E-technology social support programs for autistic children: Can they work? *World J Psychiatr* 2021; 11(12): 1239-1246
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1239.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1239

INTRODUCTION

Defining characteristics of autism

The core features of autism spectrum disorder are difficulties with social communication and restricted and repetitive behaviours[1]. However, it is commonly associated with atypical cognitive profiles, executive dysfunction, atypical perceptual and information processing, all of which vary across individuals[2]. Although the diagnostic term for autism is "Autism Spectrum Disorder", many autistic people prefer identity first language rather than person first language (*e.g.*, autistic person rather than person with autism)[3-6]. Hence, the review will use identity first language hereafter.

In Australia, approximately one in 150 people are diagnosed with autism[7]. Changes in reporting practices over time and increased awareness contribute to the increased rates of diagnosis in many cases[8-10]. Strengths and difficulties vary between individuals with autism being clinically categorised by the type of supports needed[1]. In 2018, school-aged (aged 5-20) autistic people reported the greatest difficulty they faced was fitting in socially[7]. Non-verbal communication skills account for more than 60% of overall communication ability, and has been identified as an especially important issue due to the key role these skills play in the way people socialise[11]. Studies have found that difficulties with non-verbal social skills in autistic people vary widely and include understanding facial expressions, using conversational gestures and joint attention[12-15]. Understanding these subtleties in communication plays a critical role in building trusting friendships and relationships with others, especially during school years.

UNDERSTANDING FACIAL EXPRESSIONS

Understanding and processing facial expressions is considered some of the most important non-verbal communication skills as they are often the first feature we notice when meeting other people. Faces convey important social information about our mood and intentions to those around us. An inability to understand expressions has been linked to greater difficulties in social situations[16,17]. Autistic people are observed to have significant difficulties in recognising facial expressions, and these difficulties have been found to increase over time[17-19]. Although difficulties are experienced with all six basic emotions (happy, sad, fear, disgust, angry and surprise), autistic people are observed to have specific difficulties with more complex emotions such as anger, fear and surprise.

ALEXITHYMIA IN THE AUTISTIC POPULATION

Alexithymia is a trait that occurs in approximately 5% of the neurotypical population and in an estimated 50% of the autistic population[20]. It is defined by difficulties identifying and describing one's own emotions and a lack of awareness related to physical sensations from emotions[17]. This trait is found to play an important role in interpreting facial expressions. It has been theorized that the facial expression recognition difficulties autistic people experience may actually be due to alexithymia, and not social communication difficulties[17]. However, regardless of the potential cause, the ability to interpret and respond appropriately to the facial expressions of others is important to support social connectedness for autistic people.

CURRENT SOCIAL SUPPORT PROGRAMS

Numerous support programs have been developed for children on the autism spectrum that target skill building in social-cognitive, sensory-integration and relationship-based domains[20]. In fact, many evidence-based practices for working with people on the spectrum are focused on helping social communication, play and joint attention[21]. In clinical practice, there are typically two types of programs, the first being a comprehensive treatment model such as Early Intensive Behaviour Intervention which is often organised around a conceptual framework and overarching model[22]. Such programs often require the child to participate in settings outside of their norm (*e.g.*, a clinic) and requires a minimum (20-h) time commitment by family as well as the participant. In addition, the maintenance and generalisation effects of such programs are observed to be significantly lower compared to when participation occurs in a child's typical setting[13]. The second type of support programs are those aimed at gaining a new skill or overcoming a specific behaviour; these are typically shorter programs (*e.g.*, 10–20 fortnightly sessions) until the goal is achieved. These can be manual or technology-based and include video modelling. Many video modelling programs were developed to focus on specific social-communication behaviours such as social initiation, compliment giving and conversations[23], and are seen as highly effective in helping build these skills[24].

Technology-based support programs have been organised into eight categories: computers and internet, videos, mobile technologies (mobile phones and tablet computers), shared active surfaces, virtual and augmented reality, wearables, robotics and natural use interfaces[25]. Programs delivered *via* these technologies is growing across skill areas, as they allow for on-the-go use and can complement current therapies children and adolescents may be engaged in[26-28]. In fact, van der Meer *et al*[28] suggested how portable technology such as iPads and iPhones are viable technology aids for people in areas such as communication and transitioning skills. A recent example of this technology introduced the concept of animal filters on a mobile device to understand how the idea of mind-blindness or emotion recognition can vary in contexts[29]. Other software applications or "apps" allow the user to take a photo or video while attaching specific emotions to them, which aides in recognising the emotion in the future[29].

Although there is generally no theoretical backing for the use and design of such technologies, acceptability of e-technology is high across both children and parents, with many children using iPhones and iPads almost daily[30]. Parents reportedly like the idea of tablet-based therapy, especially when it comes with in-built instructions. This is not surprising when we consider that many parents work long hours, are time poor, and struggle with the costs of taking children to regular therapy sessions[31]. Although an appetite clearly exists among parents for support programs delivered on mobile devices, a meta-analysis by Hong *et al*[32], found that there were only 14 studies with a combined 36 participants that examined tablet-mediated support programs focusing on social and communication related skills delivery. Further research has also identified that many allied health professionals do not regularly use tablet computers within their sessions[33]. This means a significant gap exists between what is currently available and what health care consumers would like to be able to access. There is a clear need for further e-technology development and research, with larger sample sizes, and targeted delivery of therapies using a variety of devices, such as tablets and virtual reality, to provide learning and simulation in naturalistic settings to lessen this translational gap.

There have been some developments in designing programs for better interpretation of facial expressions. One early development by Baron-Cohen *et al*[34]

used video modelling. The Transporters DVD targeted expression recognition by adding human faces to animated trains and to engage children in social interactions. Over time, video modelling has proven to be a viable method for helping people on the spectrum learn social skills[34]. Developments in other e-technology are still progressing. Clark *et al*[35] point out that 15 e-technology therapy-based studies were conducted between 2000 and 2016. A review identified that many tablet applications (apps) are designed as support tools with a strong focus on social skills[36]. Apps can provide flexibility of delivery of therapies using a game-based environment to be played in real-time social settings, decreasing anxiety and supporting skill development[36,37]. However, the generalisation effects for these programs were mixed, due mostly to a lack of follow up and observation outside the research setting [38,39]. A way forward would be evaluating the therapeutic benefits of e-technology support programs by objectively measuring changes in behaviour and underlying brain function that is associated with facial information processing.

TECHNIQUES FOR DESIGNING SOCIAL SUPPORT PROGRAMS

Eye-tracking

An important part of social communication is the ability to interpret social signals such as those displayed through facial expressions. Displays of emotion are generally processed by looking at the eye and mouth regions of the face, then linking the information cognitively to a social context or verbal cue. Eye-tracking technology provides a real-time objective measure of face perception and feature processing. Fixation frequency and saccadic velocity (speed of synchronised eye movements) can be mapped to provide a scan path recording. Scan path recordings in the general population show an 'upside down' triangular pattern of performance focused on the eye regions and mouth (Figure 1). Comparatively, scan path patterns for autistic people tend to show more inconsistent viewing of the facial features, with fixations mostly falling on non-salient facial regions such as the chin, ear and hairline[40]. Findings from eye-tracking technology provided important insight to why autistic people may experience difficulties interpreting facial emotions and social situations.

Findings from a number of studies report eye avoidance in autistic people and conclude a general consensus that autistic people scan faces differently when compared to non-autistic people[40,41]. Avoiding the eye area, as observed in autistic people, suggests that facial information is encoded and processed differently to their non-autistic peers[42-44]. In a meta-analysis on eye-tracking and social attention, autistic people spent less time giving attention to social stimuli compared to non-autistic people overall[45]. The research reported that this occurred more frequently when there were more people shown in the content, such as a social scene rather than a singular person. Further evidence suggests that when the facial information is coded in such a way, the greater likelihood of difficulties with social skills[46].

Specific emotions also appear to impact face processing performance. Eye avoidance (with predominant focus on the mouth region) is more frequent in autistic adolescents when specifically viewing negative emotions[47]. In a study examining angry faces, Black *et al*[44] showed that autistic children were more likely to avoid viewing angry faces and scored higher on the social communication difficulties subset measure of the Gilliam Autism Rating Scale-3 (GARS-3)[48]. Greater attention to the mouth region when viewing face images is also associated with higher rates of social anxiety[46,49-51]. Innovations in e-technology-based support programs provide a mechanism to deliver targeted supports which assist with facial expression recognition and processing difficulties, particularly those to improve eye-tracking of the most salient facial feature areas such as the eyes and mouth regions. Eye-tracking technology also allows a more objective measure of behavioural changes in face processing.

Event related potentials

Another method to explore social communication is to use electroencephalography (EEG). EEG is an electrophysiological monitoring method to measure the electrical activation in the brain in real time. This measurement is highly sensitive and can measure brain responses to the millisecond (ms) and is therefore complimentary for eye tracking researchers. It is common for these brain responses to be labelled by their polarity; either positive (P) or negative (N) due to their electrical deflection, combined with the time after stimulus onset. Additionally, these brain responses are known as event related potentials (ERPs) and are defined "as the direct result of a specific sensory, cognitive or motor event"[52]. For example, a common ERP used in emotional

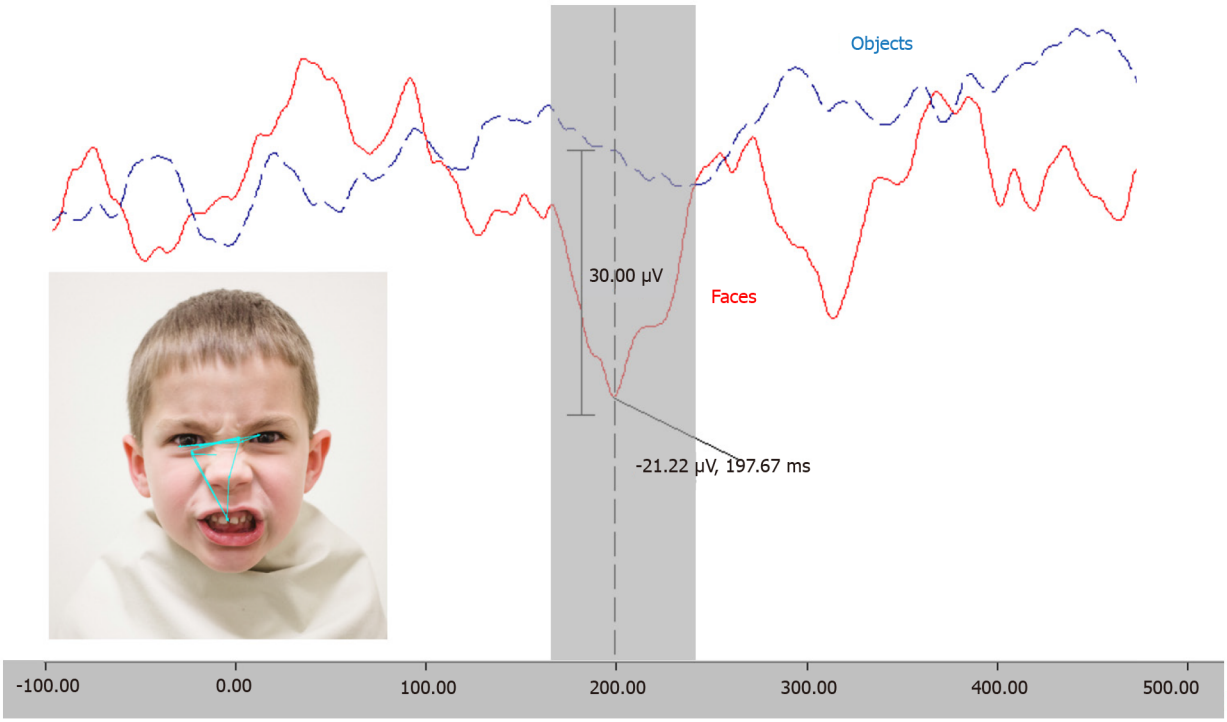


Figure 1 Event-related potentials in response to face (red) and (blue) object images of a non-autistic child. The grey area marks the face-specific event-related potential referred to as N170. Insert shows a normal scan path covering the eye and mouth region of a non-autistic child when viewing a face image.

recognition or social communication research is named the N170. The N170 ERP is observed as a significant amplitude deflection in a negative direction 170 ms after stimulus onset. Figure 1 shows the N170 in response to a face in a non-autistic child.

The N170 is a robust and reliable measure of facial recognition and has been confirmed by spatial functional magnetic resonance imaging, which demonstrates the response is generated from an area of the brain specific for facial recognition known as the fusiform gyrus. This brain region also encodes other complex visual stimuli but is most responsive when processing facial features[41]. Research has found that the N170 is not different in response to angry, fearful or neutral faces between non-autistic or autistic participants[16,41,43]. This means that the identification of a face as such is very fast, but the identification of a specific emotion expression takes longer as it requires a more detailed evaluation of the facial features and is captured by subsequent ERPs (*i.e.*, N200/P300)[53].

Autistic people usually have a slower processing time than non-autistic people when looking at facial stimuli; with slower processing times being associated with less face processing expertise[41,42,54]. Further research confirmed that there is a link between scanning the eye-region and a faster N170 response[41]. Moreover, a smaller N170 is also associated with less developed socials skills and more atypical social behaviours as is more common in autistic people[55].

CONCLUSION

Recording eye-tracking and ERPs are well suited and established methodologies that allow for a more objective assessment of support program benefits at the behavioural (eye-tracking) and neural (ERPs) level. They are less intrusive and demanding than other methods, such as functional brain imaging. As the general idea, e-technology should support these basic processes which are fundamentally involved in facial stimuli processing. The *FaceTile* task[56] is a good example of how this can be achieved, for instance, as a game-like app for autistic children. The game would ask children to recognise emotions in photographs of same-aged children. The photographs are initially covered by tiles, with the goal to remove as few tiles as possible to make a decision on the expressed emotion. The children would learn to remove tiles over the eye and mouth area to maximise their chances in doing well,

with the number of tiles over the photo increasing and becoming smaller on each level up. The aforementioned evaluation methods could then be used to test the autistic children's eye-tracking performance before and after playing the *FaceTile* game (*i.e.*, until reaching the desired game performance level). If the *FaceTile* game actually improves the face viewing strategy (*i.e.*, spending more time in the eye and mouth region) the face-specific neural processes should also improve as indexed by a larger N170 ERP compared to the pre-support program level. These measures could be further used to test possibly improved social comprehension more generally, for instance, employing tests such as the NEPSY-II[57], Cambridge Face Memory Test–Children[58], or the Social Communication Questionnaire–Current[59] before and after playing the *FaceTile* game. As such, the behavioural and cognitive measures of the application would make it a well-rounded, evidence-based program to help support autistic children to build skills in understanding facial expressions.

ACKNOWLEDGEMENTS

The authors acknowledge the autistic people and their families that have participated in the cited studies.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1247-1258

DOI: 10.5498/wjp.v11.i12.1247

ISSN 2220-3206 (online)

MINIREVIEWS

Factors related to compliance with the COVID-19 health regulations among young people

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Author contributions: Jaureguizar J, Redondo I, Galende N and Ozamiz N contributed equally to this work and wrote the manuscript; All authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they do not have conflicts of interest.

Country/Territory of origin: Spain

Specialty type: Social science

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

The coronavirus pandemic has affected all facets of our lives and all ages and social strata worldwide. Measures have been taken to protect against the spread of the virus, such as more rigorous hand hygiene, the use of face masks and social distancing. However, the focus has often been on young people, who have been seen as a group lacking sufficient respect for government-imposed measures. This review outlines the preventive measures that have been taken in different countries and discusses their specific impact on young people and adolescents, taking into account the developmental stage and concrete needs of this age group. It summarizes those studies that have provided information on compliance with preventive measures by young people and adolescents, concluding that although compliance levels among this age group are lower than among older adults, the general view of youths as non-compliant is not consistent with real, objective data. The review also summarizes different views regarding the possible reasons for this lower level of compliance, taking into account both social (gender and age) and personal factors (personality, empathy, prosociality, self-control, cognitive styles and motivations), and discusses the practical implications of these findings for the future.

Key Words: COVID-19; Health regulations; Compliance; Young people; Adolescents

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Core Tip: The effects of health regulations designed to prevent the spread of the coronavirus disease 2019 virus may be much more intense and pernicious among young people than adults. Social and personal factors, as well as the level of information to which one is exposed, peer influence and the number of elderly people one knows are factors that may help us understand why it is more challenging for

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Received: February 26, 2021
Peer-review started: February 26, 2021
First decision: May 5, 2021
Revised: June 10, 2021
Accepted: November 2, 2021
Article in press: November 2, 2021
Published online: December 19, 2021

P-Reviewer: Manenti A
S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Gong ZM



young people to comply with the established measures. This greater insight may help us design more effective preventive strategies and awareness raising campaigns, so that we can be better prepared for future crises.

Citation: Jaureguizar J, Redondo I, Galende N, Ozamiz N. Factors related to compliance with the COVID-19 health regulations among young people. *World J Psychiatr* 2021; 11(12): 1247-1258
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1247.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1247

INTRODUCTION

Coronavirus disease 2019 and health regulations

In December 2019, there was an outbreak of the coronavirus disease 2019 (COVID-19) in Wuhan (Hubei, China). At the beginning of 2020, the disease began to spread throughout China, with the rapid increase of confirmed cases and deaths soon starting to spread around the world. On January 31, 2020, the World Health Organization declared the COVID-19 outbreak a Public Health Emergency of International Concern [1].

Each country took its own measures to protect the health and safety of its citizens, contain the progression of the disease and strengthen the public health system. South Korea became the world leader in containing the virus, focusing strongly on mass testing, early contact tracking and quarantine[2]. In other parts of the world, such as China, Spain, Italy and the United States, the increase in the number of daily cases prompted governments to implement mitigation measures[3] such as stricter hand hygiene, travel restrictions, school closures and social distancing.

At the beginning of the pandemic, at least 186 countries instigated varying degrees of restrictions on population movements to curb the spread of COVID-19 and prevent health systems from being overwhelmed[4]. The first measure taken in many countries was a home lockdown and the establishment of restrictions such as allowing people to circulate on public roads only for essential tasks such as buying food, commuting to work or caring for dependents[4]. Moreover, in many countries, face-to-face educational activities were suspended in all schools and at all stages, cycles, grades, courses and levels of education, with this being one of the most widely-used measures to help maintain social distancing and decrease the contagion rate[5].

Following these restrictions, and after the incidence of the disease had started to abate, governments began to create exit strategies to unblock and re-establish "normality" in their respective countries, always in accordance with public health principles and population indicators[6]. The restrictive measures caused major economic and social disruption around the world, and governments were forced to try different exit strategies[7]. In the absence of a treatment or vaccine, some countries took measures to limit the density of gatherings. In addition to banning large concentrations of people, on a smaller scale, workplaces were obliged to establish schedules to limit crowding in offices, and healthcare facilities were forced to reduce opening hours, space out waiting rooms and offer weekend and evening appointments to accommodate and care for the most at-risk patients. Commercial establishments limited the number of people allowed in their store, and bars and restaurants reduced their capacity and even closed down during the most critical moments of the pandemic[3].

In terms of individual responsibility, behaviors in response to COVID-19 were similar to the health behaviors described by Bish and Michie[8] in relation to pandemics in general. These behaviors fall into one of three categories: preventive behaviors, which include hand washing, the use of face masks, coughing into one's sleeve and getting vaccinated; avoidance behaviors, which include social distancing; and quarantine and illness management behaviors, which refer to actions taken once a person believes they have been infected and in the case of COVID-19 includes self-quarantine[9].

In addition to being a simple and low-cost intervention, hand washing for the control of infectious diseases has the advantage of offering easy compliance as well as great health benefits. Indeed, several studies have shown that hand washing reduces

the risk of virus transmission by 55%[10].

As for the use of face masks, despite several debates about their effectiveness, in most parts of the world they have been declared mandatory in public places to prevent the spread of the virus. The use of face masks is one of the non-pharmaceutical intervention measures that can be implemented effectively without drastically altering social practices[11]. Their use in the community may also be beneficial for healthy individuals, as transmission may be presymptomatic.

Another of the measures implemented is social distancing, with scientific evidence confirming that a physical distance of at least 1 meter significantly reduces infection, and that distances of 2 meters may be even more effective. It has been demonstrated that social distancing measures prevent the transmission of the virus, thereby reducing the spread of the infection[12].

Another individual area of responsibility in the context of the current pandemic is self-quarantine. People who have been infected with the virus need to isolate themselves in order to prevent the spread of the disease. However, those who have been exposed to COVID-19 should also be isolated in order to monitor whether or not they develop the disease over time[13].

Many different health regulation measures have been implemented since the start of the pandemic. In most countries, the measures were more restrictive at the beginning and have since varied in accordance with incidence rates and hospital saturation. However, those that have remained clear and constant in many countries and have been maintained throughout the pandemic include the use of face masks, social distancing, self-quarantine and the avoidance of large gatherings of people.

The health regulation measures currently in place are therefore the main strategies used to prevent the transmission of the COVID-19 virus[14], and these measures have an important differential impact on people in accordance with variables such as age.

THE IMPACT OF HEALTH REGULATIONS ON YOUNG PEOPLE

Studies about the COVID-19 and previous pandemics have identified the fear of contamination and restricted social contact as the main risk factors for increased mental health problems[15,16]. Indeed, Orben *et al*[16] assert that "it is possible that the effects of such deprivation of social contact will extend beyond the period of physical distancing and might affect the population for years to come" (p. 634).

Social distancing may be especially challenging for adolescents and young people. Social contact is essential for developing cognition, emotions, attachment and relationships and contributes to the physiological regulation of the body's responses to acute stressors[17,18]. It is well known that peer relationships are central across the different areas of psychosocial development during adolescence and youth. As children grow older, peers become the referents around which leisure time is structured and provide emotional support and guidance in the process of growing up [19]. However, adolescence is also an especially vulnerable stage of life and is associated with strong risks for the development of mental health problems, such as anxiety and depression[20]. Moreover, the multiple hormonal and neurobiological changes that take place during this period have been linked to heightened emotional reactivity, which in turn leads to a constant need to adjust coping and stress regulation strategies[21]. Conversely, high-quality peer relationships seem to protect against mental health problems and to strengthen adolescent resilience[22].

Therefore, if we accept that young people and adolescents are at greater risk of emotional problems and that their peers are an important source of social and emotional support, it is logical to assume that the situation engendered by the pandemic may be particularly critical for them. Alivernini *et al*[23] concluded that a pandemic is a stressful life event that can have a major impact on adolescent development, especially affecting their mental health and increasing their levels of anxiety and psychological distress. Moreover, emotion regulation skills may fail when exposed to a global, ongoing stressor such as the COVID-19 pandemic, or it may be impossible to implement such skills due to pandemic-related restrictions[24].

Research has found elevated mental health concerns during the COVID-19 pandemic in comparison with time points prior to its onset[25,26]. In the specific case of adolescents, Alivernini *et al*[23] explored the positive and negative emotions of a sample of Italian adolescents before and after the start of the COVID-19 pandemic, finding an increase in adolescents' levels of negative affect following the national lockdown and a decrease in their levels of positive affect. These results are consistent with those found by Rogers *et al*[27] among United States adolescents, with the authors

arguing that the pandemic may have challenged the psychological and coping resources of adolescents and young people, leading to fluctuations in underlying mood states and rendering them more vulnerable to mental health problems.

A qualitative study carried out in the United Kingdom, which explored public perceptions and experiences of social distancing and social isolation related to the COVID-19 pandemic, found that frustration or anxiety over loss of social interaction and fears over the duration of social distancing and isolation measures were all major worries[28]. A similar study also identified participants' concerns about not being able to socialize face-to-face with their peers as well as their willingness to participate in the response and recovery process as a means to make their voices heard[29].

In response to this lack of face-to-face interactions with peers and the decrease in leisure time spent in large groups with friends, young people and adolescents have increased the time they spend on social media and the internet. The use of screens has increased considerably, not only because it is a way of interacting with peers but also because it has been the means of communication to which many schools and universities have had to resort. Some studies have asserted that adolescent use of digital technologies and social media might mitigate some of the negative effects of physical distancing[16]. In contrast, however, previous studies have identified certain risks linked to the excessive use of screens, such as poor sleep, higher accumulated time spent sedentarily and exacerbated risk for mental health problems[30]. Indeed, the study by Larcher *et al*[29] mentioned above identified some concerns among young people about the significant amount of screen time to which they are now exposed during the pandemic. In this respect, Orben *et al*[16] suggested that the types of technology used by young people should be taken into account since engaging in direct communication may increase wellbeing[31] and help maintain personal relationships[32], whereas passive use of social media has been related to negative effects (social comparison, envy, *etc.*)[33]. Moreover, the effect information and communication technology use at all levels of education has had on pupils' academic and holistic development remains to be seen.

On a more optimistic note, increased family time may be one of the positives that can be taken from the critical situation to which the pandemic has brought us. The fact that young people and adolescents have spent more time with their families may have mitigated the effects of the drop in social face-to-face interactions with peers. In particular, adolescents who have positive relationships with their parents or caregivers may be less affected by physical distancing than those who do not or who are living alone[16].

COMPLIANCE WITH HEALTH REGULATIONS AMONG YOUNG PEOPLE

Compliance rates

Adolescents and young adults are internationally considered to be the potentially least compliant age group in relation to the measures established by different governments, especially those involving social distancing[34].

This had already been found prior to the pandemic in relation to other health-related behaviors[35,36]. In contrast to the younger population, a study conducted in May 2020 found that the older population was the one that engaged most in protective health behaviors[9].

But let us examine the compliance rates reported to date. For example, in a study conducted with 683 adolescents (13-18 years) from the United States, Oosterhoff *et al* [37] found that most youths were engaging in social distancing a lot (26.9%) or a great deal (56.6%), with fewer engaging in social distancing somewhat (13.0%) or a little (3.5%).

Similarly, a longitudinal study that was already collecting data in Zurich prior to the pandemic (in this case with 737 young adults) found that non-compliance was somewhat higher for hygiene-related measures than for social distancing, but even so, non-compliance levels were low[34].

In another study, also carried out in Switzerland but in this case in another canton [38], the authors observed high self-reported adherence to rules (85%), which increased significantly with age and level of worry.

In Oslo (Norway), 12686 secondary school students were found to have high percentages of compliance with the regulations. Most of them exceeded 70% compliance, with hand washing (84%) being the rule most frequently complied with. However, the compliance rate for physical distance (50%) was considerably lower[39]. In other words, although it is true that most adolescents comply with the established

rules, the greatest difficulty seems to be in maintaining social distances, something which, as has already been pointed out in previous sections, is especially difficult during a developmental stage such as adolescence. Nevertheless, Rieger[40] found high levels of compliance with even social distancing among 250 university students in Germany.

In light of the findings outlined above, it seems that the prevalent pessimistic view of young people's compliance rates is inconsistent with real, objective data. This is similar to what Raude *et al*[41] observed about France. Underlying this may be the fact that everyone feels they are complying much more than everyone else with the established regulations. In this sense, it is worth noting the study by Shelby *et al*[38] which observed a discrepancy between respondents' perceptions of their own compliance (85%) and their perceptions of others' compliance (65%).

Nevertheless, even if non-compliance is not always as high as is often perceived, it may be interesting to determine the factors behind both compliance and non-compliance with the aforementioned measures.

Explanatory factors

At this point, it may be worth mentioning both more immediate factors that explain why people do not comply with the measures and not so immediate previous risk factors, which at both a personal and social level may be influencing this lack of compliance. Regarding the former, variables such as the perception of risk, the search for information, trust in the government and the perception of compliance with these measures as a moral obligation are related to a higher level of respect for them (see studies cited by Nivette *et al*[34]).

In their own study, Nivette *et al*[34] distinguished between internal (such as wanting to protect oneself and others) and external factors (such as having social events cancelled) for social distancing compliance. Likewise, they identify a series of barriers that can lead to non-compliance with this measure, including feelings of sadness derived from loneliness or the inability to work remotely. Fortunately, aspects such as misconceptions and/or conspiracy theories yielded practically residual data (1%-3%), suggesting that despite the attention these issues sometimes receive in the media, they do not really seem to be a major reason for failing to comply with the recommended health measures.

Among the variables mentioned above, the one that seems to stand out from the others is trust in the government, which largely determines the population's compliance with the different preventive measures in countries such as France[41] and Japan, to cite only two.

In relation to the not so immediate pre-existing aspects, which can be considered more long-term risk or protective factors, two types can be distinguished: social factors and personal factors.

The most widely studied social factors have been gender and age. For example, it has been found that women generally comply more than men with the established public health measures[34]. This was also found in Spain in a study carried out during the weeks of severe lockdown[42] as well as in France where it was found that men, as well as young adults, were less likely to follow the guidelines established to curb the spread of the virus[41]. This second finding is also linked to the other psychosocial variable mentioned above, namely age.

Numerous studies highlight age as a key variable for compliance with preventive measures; in some cases, even after controlling for the effect of other factors[43]. Nivette *et al*[34] found that people over 45 years of age were significantly more compliant with social distancing than those aged 18-24. These results are consistent with those reported in Spain during the severe lockdown by Gutiérrez *et al*[42]. These authors found that the age groups most likely to break the rules were those between 20-30-years-old and under 20-years-old, which had non-compliance percentages of 32.7% and 23.3%, respectively. Similarly, Margraf *et al*[44] point out that there are countries, including Spain, in which younger people show less adherence to norms than other age groups.

With respect to personal variables, one of the factors that has been studied regarding non-compliance with health measures among the adult population in general is personality, specifically aspects such as high levels of the so-called dark triad traits (machiavellianism, narcissism and psychopathy) or low levels of agreeableness[45]. These are known as antisocial traits and have been studied by Miguel *et al*[46] in a large sample of Brazilian adults (n = 1578), with the results indicating (as expected) that people with an antisocial pattern profile found it more difficult to comply with the measures than those with an empathy pattern.

The same can be said for people who avoid risk and are more prone to health/safety behaviors. In times of the pandemic, these people tend to adopt measures such as social distancing and mask wearing[46,47] or tend to reduce their mobility[48,49] to a greater extent than those with a risk attitude.

Coroiu *et al*[14] discuss the role of empathy and prosocial behavior as well as the barriers and facilitators of compliance. Moreover, a series of studies conducted with 3718 people from Germany, the United States and the United Kingdom has found that fostering empathy for those most vulnerable to the virus encourages adherence to prevention measures[50].

Likewise, level of self-control also seems to have a significant influence on compliance with the established preventive measures. People with higher levels of self-control comply to a greater extent with rules such as social distancing or the use of face masks, and the weight of this factor remains significant even after controlling for other factors such as political ideology or demographic variables[47].

Xu and Cheng[47] also identify another personal variable, in this case of a cognitive type, which influences compliance with preventive measures: need for cognition, understood as a tendency to seek information and engage in systematic thinking that increases decision-making competence. This variable has previously been associated with other healthy behaviors, such as being informed about AIDS or adopting a positive attitude towards condom use[51]. In the context of the current pandemic, need for cognition is understood as a personal variable associated with a higher level of compliance with measures such as social distancing and face mask wearing.

Another psychological factor that may influence compliance is the time perspective [52], defined by Sobol *et al*[53] as "a cognitive style involving a tendency to focus on a particular segment of time: past, present or future" (p.2). The "carpe diem" perspective (focused on the here and now, in the sense of being aware that what one does at this moment has an influence on the future situation) has been found to be the best predictor of compliance.

All the factors described so far refer to the population in general, but what can be said about the younger generations in particular? Is there any factor that explains the level of compliance with preventive measures among this segment of the population?

One of the variables that has been studied in relation to both youths and the general population is gender, although the conclusions are as yet unclear. For example, in a study carried out with young adults in Switzerland, a higher level of non-compliance was found among men in terms of total scores on the hygiene, social distancing and general non-compliance measures. However, a more detailed examination of the results revealed no differences between men and women in many of the specific aspects of each measure[34].

Oosterhoff *et al*[37] analyzed motives for respecting social distancing norms in a sample of 683 American adolescents aged between 13 and 18 years from the perspective of Self-Determination Theory[54]. According to this theory, the motives that prompt a person to act in a certain way may be externally controlled (*e.g.*, obeying imposed rules) or autonomous (volition-based). A priori, autonomous motivations are more closely associated with prosocial behaviors than controlled motivations[55] as well as entailing greater benefits in terms of mental health for the person who puts them into practice[56]. These reasons were the ones most commonly reported by the participants in the study. Specifically, "youths most commonly referenced prosocial motivations, including social responsibility (78.1%) and not wanting others to get sick (77.9%), to engage in social distancing"[37], although controlled motivations were also common. Similar results were found by Alivernini *et al*[23] in a longitudinal study with Italian adolescents.

In relation to those rules with which we are often obliged to comply, prior to the pandemic it was found that young people with characteristics of the so-called antisocial potential[57] are more likely to break the rules, and the scientific evidence gathered in times of the pandemic also seems to be consistent with this. For example, impulsivity and certain personality traits such as amorality, egoism and psychopathy are associated with greater non-compliance with health measures[58]. For their part, Alivernini *et al*[23] report that of the personality-related aspects they analyzed, only one, openness to experiences, was found to have a statistically significant relationship with physical distancing behavior. Specifically, the results indicated that adolescents who were more non-compliant with the social distancing norm were those who were more attracted to risk, although this association was weak.

Another variable that has been identified is peer influence, which is particularly important (both negatively and positively) during this vital developmental stage[59] and may be an aspect to take into account in the future when attempting to design campaigns that really manage to convince this age group of the importance of

complying with health measures.

For their part, Sobkow *et al*[60] focused on risk perception and the cognitive and emotional factors that may influence it, studying the impact of variables such as affect, mental imagery, controllability, self-efficacy and numeracy.

In a study carried out with 2130 Chinese adults (university students), Guo *et al*[61] analyzed the individual and environmental factors that may be behind compliance with social distancing rules. The individual factors identified included variables such as gender, depressive symptoms and psychological distress, whereas the influence of social media was the principal environmental factor found, with people who spend less time informing themselves online being more vulnerable due to their limited knowledge of the measures required to stay safe.

Finally, another factor that seems to influence the younger population's compliance with health measures such as social distancing is the number of elderly people they know personally[40]. This may be relevant when designing and implementing prevention programs aimed at this segment of the population.

Table 1 summarizes the main findings on factors related to the level of compliance with COVID-19 prevention measures.

CONCLUSION

The emergence of the COVID-19 pandemic at the beginning of 2020 plunged the world into an unprecedented situation, with implications in all spheres of people's lives. In order to cope with this crisis and curb the spread of the virus, governments in different countries took measures, which were generally stricter at the beginning of the pandemic (*e.g.*, lockdown) and have since been relaxed as contagion and death rates and pressure on healthcare systems have decreased[6]. Nevertheless, some restrictions, such as the use of face masks, hand washing and social distancing remain in force in many countries, and until vaccines and treatments begin to have a clear impact, compliance with these rules will continue to be key elements in the struggle to keep the situation under control.

In this regard, it should be noted that adolescents and young people have been internationally identified as the age group least committed to compliance with these measures[34,42,44]. However, it is important to understand that given the characteristics of their developmental stage (*e.g.*, need for greater contact with peers for their cognitive, social and emotional development), compliance is particularly difficult for them. Moreover, it should not be forgotten that adolescents and young people are more vulnerable to mental health problems[20], and limitations on social contact put them at even higher risk[22]. One way or another, what is certain is that it is not yet possible to anticipate how long physical distancing measures will remain in place and how they will affect adolescents' and young people's development and mental health in the longer term. Although social distancing measures are temporary, several months of physical distancing represent a large proportion of a young person's life during a sensitive period of development, and in this sense, the effects may be much more intense and pernicious than among adults. Furthermore, we still do not know how other stressors stemming from this crisis will influence adolescents and young people in the future (economic pressure, uncertainty, cancellation of public events marking key life stages and rites of passage, *etc.*)[16]. Finally, although technological devices enable relationships to be maintained at a distance and bring people closer to their peers, their excessive use also has negative consequences[30], and they should not, therefore, be viewed as the only alternative.

As for the factors that influence compliance or non-compliance with established measures, the few studies that have been published to date point to a wide range of different elements that still require further research and in-depth study. For the moment though, it seems that lower compliance is associated with factors such as being male and being young as well as with having an antisocial personality pattern, a low level of empathy, a low level of self-control or a certain tendency to engage in risky behaviors. The level of information to which one is exposed, the influence of peers and the number of elderly people one knows also seem to play a role. Although explanations of the influence of these factors are still tentative, they point the way for further research. Moreover, it is interesting to consider these factors as possible foci for interventions in the long term. Indeed, many of the factors identified can be modified or improved: for example, self-control can be strengthened with practices such as delayed gratification[62,63]; news report and message framing may affect how people evaluate the risk of an incident or situation[64,65] and may therefore be useful for

Table 1 Explanatory factors for compliance/adherence to coronavirus disease 2019 measures

Factor types	Factor sub-types	Specific aspect	Adherence/compliance	
Immediate factors		Trust in the government	Higher level of trust	Higher compliance
		Perception of risk	Higher perception of risk	
		Search for information	More search of information	
		Perception of compliance with rules	Perceiving compliance as a moral obligation	
Previous risk-factors	Social factors	Gender	Women	Higher compliance
		Age	Older people	
	Personal factors	Personality traits	Machiavellism	Lower compliance
			Narcissism	
			Psychopathy	
			Antisocial traits	
		Risk taking	More risk taking	
		Empathy and prosocial behavior	Higher empathy and prosocial behavior: higher compliance	
		Self-control	More self-control: Higher compliance	
		Need for cognition	Tendency to seek information and to follow a systematic thinking	Higher compliance
		Time-perspective	"Carpe diem" perspective	
		Motivation	Autonomous motivation	
		Influence of peers	Depending on peers' attitudes	
		Number of elderly people one knows	Higher number	

addressing risky attitudes[40]; and emphasizing relations with the elderly may help raise awareness and enhance empathy towards this population group.

However, although the contribution of these individual factors is of great interest, when thinking about preventive strategies or awareness raising campaigns, it is important to include interventions that will impact a large number of people since individual variables are usually difficult to modify, even more so in such a short period of time as that required to curb the spread of a virus. It is particularly important to continue with an exhaustive study of all the factors that facilitate or hinder compliance with social distancing measures ("stay-at-home" or "shelter-in-place" orders), given that these may potentially be required for months or even years[14] and involve significant lifestyle changes. One possible strategy for encouraging these behaviors would be to provide the population with real data on those who do not comply with the measures, of whom there are far fewer than generally believed[41]. This would perhaps encourage people to consider non-complaint behaviors as isolated and non-representative events, which would in turn decrease the general frustration felt by those who make the effort to comply as well as increasing social criticism of these attitudes.

In relation to the specific ways in which preventive or intervention campaigns can be implemented, some authors highlight the need to identify which groups are at greater risk of non-compliance with the rules in order to design social marketing strategies or policies that are customized and adapted to their specific characteristics [66]. The basic argument is that if we want standards to be effective, we cannot simply direct them at the entire population and expect everyone to comply. Rather, an effort should be made to adjust them to different social groups and their particularities.

To facilitate this last point, and given that adolescents and young people are one of those groups with a lower level of compliance, many authors and studies have already pointed out the importance of giving youths a voice and involving them in strategic plans for restructuring the policies, systems, workflows and communities affected by COVID-19. The idea is that they should not perceive the measures as something

imposed by adults or institutions, and therefore far removed from their own world, but rather as something worth getting involved in. It is therefore advisable to give adolescents and young people the autonomy to develop and deliver their own campaigns through social media, for example, supported by influencers and/or people who are relevant to them[60]. We should validate the passion felt by youths to regain normalcy while at the same time encouraging, empowering, and engaging them in forming creative solutions for a new normal.

Finally, it is important to note that although the future of the coronavirus crisis looks brighter every day, the reality is that we will continue to have to live with these measures for some time yet to come. It is therefore essential to apply the knowledge we are gaining to the way in which we deal with this pandemic, until it finally comes to an end, and to take advantage of all these ideas and resources to prepare for other social and health crises that may occur in the future.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1259-1266

DOI: 10.5498/wjp.v11.i12.1259

ISSN 2220-3206 (online)

MINIREVIEWS

Mechanism of olfactory deficit in neurotrauma and its related affective distress: A narrative review

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Author contributions: Logan M, Kapoor S, Peterson L, Oliveira M, and Han DY all collected the literature review and wrote the manuscript.

Conflict-of-interest statement: None.

Country/Territory of origin: United States

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative

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Abstract

Traumatic brain injury (TBI) is among the leading causes of death and disability all over the globe. TBI is also commonly associated with clinical sequelae of posttraumatic depression, and reports of other subsequent affective distress are common. Similarly, posttraumatic changes in chemoreceptive sensory functions, primarily due to coup-contrecoup injury induced shearing of the olfactory nerve fibers, leading to anosmia and ageusia are also well documented in the literature. However, the current literature is limited in addressing the intersections between said variables. The aim of this study was to provide a focused narrative review of the literature, to address these intersections found in clinical sequelae of TBI. As chemoreceptive sensory deficits are also linked to significant affective distress of their own, this review addresses the bidirectionality between sensory deficit and affective distress. Prevalence, demographics, mechanisms, and clinical implications are presented. Previous research is presented and discussed, in an effort to highlight the importance of consideration for all factors in TBI patient care and future research.

Key Words: Brain injuries; Brain injuries, traumatic; Anosmia; Depression; Affective symptoms; Smell

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Received: March 31, 2021
Peer-review started: March 31, 2021
First decision: July 15, 2021
Revised: July 29, 2021
Accepted: November 13, 2021
Article in press: November 13, 2021
Published online: December 19, 2021

P-Reviewer: Mehraeen E
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

Core Tip: In neurotrauma, coup-contrecoup injury induced shearing of olfactory fibers commonly leads to bilateral anosmia or severe hyposmia, and related ageusia. Post-traumatic sensory loss and depression are common in patients. All three variables' intersections in traumatic brain injury's clinical sequelae are discussed.

Citation: Logan M, Kapoor S, Peterson L, Oliveira M, Han DY. Mechanism of olfactory deficit in neurotrauma and its related affective distress: A narrative review. *World J Psychiatr* 2021; 11(12): 1259-1266
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1259.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1259

INTRODUCTION

Traumatic brain injury (TBI) has been consistently connected to a broad spectrum of pathologies including post-injury cognitive and sensory deficits[1]. According to the Centers for Disease Control and Prevention's (CDC) most recent statistics, TBI is responsible for approximately 2.9 million hospitalizations, emergency department (ED) visits, and deaths in the United States alone[2,3]. Within those 2.9 million cases, nearly 1 million of them were in children[2]. TBI related ED visits rose 53% from early 2000's to mid-2010's, and most signs point to these numbers continuing their annual rise in the future with only minor fluctuations[2,3]. The age group with the highest rates for TBI are ages 75 and older[2]. Additionally, the leading cause of TBI related deaths change for each age bracket. For ages 0 to 4, the leading cause for TBI related death was homicide. For ages 15-24, 25-34, and greater than 75 years, the leading cause was motor vehicle accidents. The leading cause for 45-64 years old is intentional self-harm. Finally, falls accounted for the highest rate of TBI related death for age 65-74[2].

TBI can range from mild effects, such as transient mental status changes, to lasting deficits in motor skills, sensory perception, and cognitive ability[1,2,4]. Because of the wide range in severity of TBI symptoms, there is an extensive amount of literature and research within the scientific community into the etiology, pathophysiology, symptoms, and treatment options for TBI. However, an often-overlooked side effect which can be attributed to TBI is olfactory disturbance (OD). Due to the mechanism and the biophysics of acutely rapid acceleration immediately followed by deceleration associated with TBI (coup-contrecoup injury), the olfactory bulbs and the olfactory epithelium are at high risk for damage *via* exogenous trauma induced shearing[5,6]; as the severity of the TBI increases, so does the risk of OD. Recent literature shows OD incidence rates (specifically anosmia) of 9.5% for mild TBI, 20% for moderate TBI, and 43.5% for severe TBI[5].

When attempting to understand the cause-and-effect relationship of TBI's direct association with OD, it is important to discern the role of head trauma as one of the main origins[7,8]. As noted in the extent literature, there are varying degrees of dysfunction encompassed by the TBI diagnosis, many of which depend on the localization of injury[9]. This has been found to be the case with OD as well, given that not all parts of the brain known to play a role in the process of olfaction are isolated to one specific area[8,10]. In instances of cerebral neurotrauma, there is a greater chance of damage to the olfactory bulb and other anterior structures, such as the olfactory cortex (OFC)[11,12]. If the trauma is more severe and diffuse in nature, there is a greater chance of disruption to sensory integration pathways, located in more posterior sections of the brain[13]. A common result of damage to the olfactory integration chain often manifests as parosmia, a dysfunction in the specificity of smell detection[14]. The replacement of normal, appetizing food aromas with repugnant odors, more associated with malodorous substances[14], is an applicable example. There is no one exclusive type of impairment or location of damage across all TBI patients[15]. Given the strong association of OD with TBI, we can conclude that multiple variants of OD can exist, particularly when considering the effects of coup-contrecoup injury[7,11,14,16].

The types of dysfunction classified as OD can range from a simple difficulty in recognizing aromas, to further disruptive forms of parosmia, and even complete anosmia or absence of olfactory perception[7,14,16]. There are multiple mechanisms for post-traumatic OD. The most common etiology, however, is related to the

"anterior-posterior movement" of the brain in relation to the interior of the skull itself, from prior mentioned coup-contrecoup injury[7,11].

OD's severity can vary greatly, typically categorized as either total loss of smell (anosmia), decreased smell sensitivity (hyposmia), or altered sense of smell (dysosmia/parosmia). OD is a prevalent condition in the United States, with an estimated rate of 10%-15% in adults over the age of 40 having disrupted smell in any given year[5,17]. When there is a sensory disturbance as prevalent as OD, we must also assess other potential subsequent problems that can come secondary to OD. A significant association to OD is depression and related disorders. Both depression and OD have neuroanatomical structures that contain common layers[18]. However, the similarities between these anatomical substrates lead to more complications in clinical differentials. Not only can depression be secondary to OD, but the inverse can also be true. In addition to developing depression post-OD, olfactory functioning can also be negatively impacted by depressive states[18], rendering this "chicken or the egg" phenomenon a challenge in accurate clinical differentials.

TBI is also associated with an increased risk of depressive symptoms. Depression has been a well-known clinical sequelae of TBI and the literature on this topic has been established for decades[19]. Additional literature also has been illustrating how clinicians can improve their diagnostic clarity for major depressive disorder (MDD), as well as how much loss of consciousness (LOC) can play a role in the severity of MDD symptoms and overall cognitive functioning[20,21]. While the estimated rate of depression in TBI patients does vary greatly (anywhere from 6%-76%), the literature has established that the incidence of MDD within the TBI population is significantly higher than the general population[21-23]. Nonetheless, given the wide range of current prevalence estimates, continued pursuit of controlled studies to address said variance is needed.

TBI AND SENSORY LOSS

As supported by the literature, the volume, or amount of gray matter and associated neurological connections within the olfactory bulb, has been associated with varying levels of functionality[9]. In patients with a decreased olfactory bulb volume, there is a strong correlation with decreased olfactory function, as evidenced by poor performance on various multi-modal examinations[14,24]. This trend of decreased olfactory capacity is augmented by the presence of TBI, or more specifically, its location and severity[14,15]. As noted previously, in patients with more diffuse neurocognitive injury, there is an increased chance of greater complexity in OD, relative to frontal lobe damage and resulting anosmia[14].

Incidence rates for complete anosmia after TBI range from 9.5%-43.5% and are highly correlated with the severity of the TBI[5]. This is compared to the approximately 20 million adults over age forty in the United States who suffer from OD[25].

In considering TBI as a primary source of OD[7,8], it is estimated that an approximate one-year recovery period exists, where the patient has the potential to gradually regain any function that was otherwise lost or impaired by their TBI. This is however, also often followed by a plateau of functional re-acquisition[15]. Similar to the global phenomenon witnessed in TBI patients, individuals with OD, specifically, may gradually regain their olfactory functionality[26,27]. This has been hypothesized to be related to the synaptogenesis of nerve cells connected to the areas damaged by the TBI, such as the olfactory bulb or OFC[28].

The olfactory system is a complex network of systems that make up one of the oldest sensory modalities of mammals[29]. The olfactory epithelium is found on the superior medial vertical lamellae of the superior turbinates, and is made up of three different types of cells: Basal, supporting, and olfactory receptor[29,30]. The olfactory system experiences consistent turnover and regeneration of its adult neurons[29]. A key part of the olfactory mechanism is the olfactory bulb, which receives the signals from the olfactory epithelial cells and continues the communication process for olfaction to be executed[30,31]. As mentioned prior, when the nerve fibers of the olfactory receptor cells are sheared or stretched from the coup-contrecoup injury, they are no longer connected to the olfactory bulb[30,31]. This leads to the disruption of sensory signals within the olfactory pathway, resulting in anosmia[5,25,30].

The epithelial cells present within the olfactory system are the only known neuron group that possess the ability to regenerate when damaged, contingent to the integrity of the olfactory bulbs[25,29]. Costanzo[31] states that "the olfactory epithelium retains its capacity to undergo neurogenesis long after development", and that the degree of

neuronal recovery varies with the severity of the injury. There are multiple barriers to effective regeneration, including spatial challenges from disruption of axon sheath alignments, fibrosis over the olfactory bulb, and/or broken synaptic sites[31]. With multiple challenges, it becomes exponentially complex for the neurons to reconnect to the olfactory bulbs. This likely explains a correlation between the severity of the TBI and the difficulty of functional recovery of olfactory senses (Figure 1).

Currently, many modalities and tools exist to identify the various forms of neurological disruption. Psychophysical and electrophysiological assessments, in addition to neuroimaging techniques, are among the tools used to diagnose OD[32-35]. In recent years, however, a more advanced form of imaging has garnered interest for its ability to scan restricted areas of the brain with more precision[32]. Known as diffusion tensor imaging (DTI), has already demonstrated itself to be a useful tool, capable of providing enhanced insight into the etiopathogenesis of the neurological disruption associated with OD[13].

DTI employs fractional anisotropy, the indices of the diffusion of water molecules across white matter tracts in the brain[13,32], in comparison to more established, de facto neuroimaging. This technique provides a more detailed, *in vivo* quantification of nerve fila and white matter microstructure, down to the individual nerve fibers[36,37]. In terms of its relevance to OD, medical professionals now possess the ability to illustrate the severance of nerve fibers from the olfactory bulb or other essential areas that play a role in the sensory integration of olfaction[12,13,32]. This enables the visualization of minute or gradual regrowth that is often missed by other forms of neuroimaging[13].

A 2017 study by Bonanno *et al*[13] focused on the role that DTI may play in the treatment of TBI and related OD; more specifically, the discrepancy between MRI and DTI were highlighted[13]. Both of the imaging techniques were performed within the same time period, first at baseline shortly after the TBI and then again, at 1-year status/post[13]. MRI demonstrated the presence of encephalomalacia, while the DTI scan was remarkably able to reveal significant axonal regrowth in both the left and right hemispheres[13,38]. This was demonstrated by as much as a 142% increase in average length of fiber tracts within the right hemisphere alone, relative to a baseline scan performed shortly after the TBI[13]. A 112% increase in the overall number of fiber tracts was also observed[13]. While DTI may be an effective tool in tracking white matter changes in the brain, additional studies utilizing the imaging technique for the examination of OD, in particular, are needed[13].

SENSORY LOSS AND DEPRESSION

Depression is common in the population, with estimates that 8%-12% of individuals in the United States will be affected by depression at least once in their lifetime[39]. The 2017 study published by the National Survey on Drug Use and Health revealed that the prevalence of a major depressive episode in adult females (8.7%) was significantly higher than adult males (5.3%) when accounting for sex, and that the 18-25 age bracket is home to the highest prevalence rate (13.1%) when accounting for age. In addition, individuals who reported two or more races had the highest rates (11.3%) when accounting for race[40]. In 2017 alone, 4.5% of the United States adult population experienced at least one major depressive episode with severe impairment, which also made up approximately 64% of major depressive episodes[40]. These statistical trends continue when looking at adolescents, but all of the prevalence rates are increased[40]. This shows that depression is still a prevalent issue in society and most people who are experiencing depressive episodes have severe impairment.

The literature also illustrate links between sensory loss, specifically olfactory functioning, and various mental health conditions including schizophrenia[17,39]. Deems *et al*[41] studied the relationship between depression scores and OD patients revealed that sensory dysfunction influences quality of life[41]. Subsequent studies have been conducted to explore the relationship between depression and OD. However, most of these studies have shown mixed results, which is likely related to inconsistency within the study populations[17,39,42]. While some studies focused on people reporting primary olfactory loss, others included patients with primary depression.

Despite the need for ongoing research to clarify the exact relationship between OD and depression, we can still deduce many things from this relationship. We know that when the olfactory bulb suffers from reduced input, there is a clear negative relationship with neurotransmitter concentration, leading to the potential disturbance

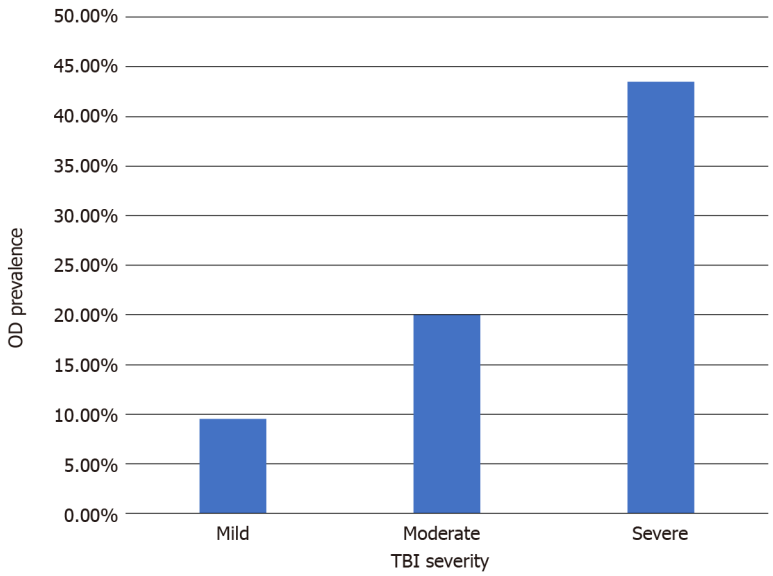


Figure 1 Olfactory disturbance prevalence by traumatic brain injury severity. OD: Olfactory disturbance; TBI: Traumatic brain injury.

of emotional functioning[18]. Additionally, olfactory functions are highly involved in emotion and memory due to signal exchanges from the olfactory bulb to the hippocampus and amygdala[39]. There is also a correlation between OD and depression symptoms that is mediated by the severity of the loss of smell[17]. Based on longitudinal studies, there is a predictive relationship between one month follow up parosmia scores and six month follow up depression and anxiety scores[42]. It has also been demonstrated that treatment for OD can lead to a decrease in depression scores, even if more replication is needed to increase confidence in that claim[39]. There is also evidence for clinicians to include both affective and olfactory assessments in TBI cases, as it can aid in the prediction of affective outcomes[42]. In summary, there is a bidirectional relationship between sensory loss and depression.

In addition, the recent coronavirus disease 2019 (COVID-19) pandemic has led to some further development in research, especially in the context of sensory loss. It is well known to most that sensory loss, primarily smell and taste, is among the more prevalent symptoms of COVID-19[43]. Other neurological injuries can also occur following COVID-19 infection, including strokes, that can impair affective and sensory functioning[44]. While researches on reinfection rates, mortality predictors, and electrocardiogram readings are still being investigated, there are affective concerns that should continue to be addressed[45-47]. Within the context of affective distress with known COVID-19 related symptoms including anosmia, self-care remains critical prior to regain of function back to baseline[48]. It is worth investigating whether this COVID-19 related sensory loss will hold the same link between olfactory sensory loss and long-term affective distress as discussed above.

TBI AND DEPRESSION

TBI accounted for nearly 3 million ED visits in 2014, which was up from 1.2 million in 2006, and has been experiencing steady increases in its annual death rate and hospitalization rates[1,9]. Recent estimates show that the annual financial cost of TBI associated problems is more than 56 billion dollars[22]. In addition to this great financial cost, there is also a high risk of developing symptoms of depression, impaired life satisfaction, and various chronic disabilities[2,19-23,49]. Once the age bracket where TBI is most common (age 75+) is compared to the prevalence rates of depression (ages 18-25), it is easy to see these risky age groups tend not to overlap[2,23,40]. Despite this, we are seeing an increase in depressive rates within TBI patients which tend to be significantly different than the general population rates. Depression also negatively impacts proper recovery trajectory after a TBI[19].

Within TBI patients, some experience a LOC and others do not lose consciousness, with the odds of experiencing a TBI with LOC increasing based on several factors, including TBI severity and various biological and social factors[20,22,50]. One study that analyzed the 2014 data from the Ohio Behavioral Risk Factor Surveillance System

showed that 21% of adults reported to have at least one TBI with LOC in their lifetime [50]. That same study showed that various factors associated with an increased reporting of TBI with LOC included lower income, being male, age, and unemployment status[50]. Additional studies have shown that TBI (both with and without LOC) contributes to increased depressive symptoms, lower cognitive functioning, and risk for lifelong neuropsychiatric concerns[20].

It is critical for clinicians to better understand the relationship between TBI and MDD in order to better serve their patients and assist the patients on their road to recovery. Even though many physicians are aware of the link between these two diagnoses, the diagnosis of MDD when a patient is experiencing disturbed mood after a TBI remains a more complex concern. Due to the additional diagnostic criteria of MDD and the differential diagnosis between MDD and the other depressive disorders, many physicians can easily misdiagnose a TBI patient's affective concerns[21]. More research is needed in this area to show how to qualitatively and quantitatively improve the accuracy of mood disturbance diagnoses within TBI patient population.

CONCLUSION

As one of the world's leading causes of death and disability, TBI is a highly complex clinical phenomenon. With the bidirectionality of sensory loss and depression, as they are among some of the more common clinical sequelae of TBI, these clinical presentations themselves further complicate posttraumatic prognosis and related treatment planning. In milder injuries, said symptoms can be assessed to assist in differentials, prognostic implications, and guidance for acute therapeutic regimen. In more moderate and severe injuries with permanent injury sequelae, said symptom assessments can also assist with long term care planning, along with guided therapeutics for quality of life improvement. As the literature continues its pursuit in the study of TBI mechanisms, it remains imperative that direct and peripheral symptoms like olfaction and related gustation, affective distress, and their bidirectional implications are continuously investigated, beyond the traditional pathophysiological mechanisms. As this study was formatted as a focused topic narrative review to investigate TBI related sequelae, the study is limited in the quantity of systematically reviewing the TBI variables highlighted in this study. Recommendations for future studies include systematic analyses and review of the literature, meta-analyses, and controlled studies to further assess the bidirectionality of sensory loss and affective distress in TBI.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1267-1273

DOI: 10.5498/wjp.v11.i12.1267

ISSN 2220-3206 (online)

MINIREVIEWS

Physical activity and mental well-being during COVID-19 pandemic

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Author contributions: All authors conceptualized, designed the study, and wrote the first draft of the manuscript; Abdelbasset WK managed and supervised the literature searches; all authors reviewed and agreed to submit the final version of the manuscript.

Conflict-of-interest statement: No competing interests to disclose.

Supported by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fast-track Research Funding Program.

Country/Territory of origin: Saudi Arabia

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

The corona virus disease 2019 (COVID-19) pandemic has resulted in most nations deciding upon self-isolation and social distancing policies for their citizens to control the pandemic and reduce hospital admission. This review aimed at evaluating the effect of physical activity on mental well-being during the COVID-19 pandemic. It was concluded that the COVID-19 pandemic may lead to augmented levels of angiotensin-converting enzyme (ACE)-2 that led to cardiovascular and neurological disorders associated with highly inflammatory effects of viral infection affecting the brain tissues leading to damage of the nervous system and resulting in cognition dysfunction, insulin sensitivity reduction, and behavioral impairments. Anxiety and depression may lead to negative effects on various quality of life domains, such as being physically inactive. Regular physical activities may reduce inflammatory responses, improve ACE-2 responses, and improve mental well-being during self-isolation and social distancing policies related to the COVID-19 pandemic. Further studies should be conducted to assess the different intensities of physical activities on cardiovascular function, and mental well-being during the COVID-19 pandemic.

Key Words: COVID-19; Physical activity; Mental well-being; Pandemic; Angiotensin-converting enzyme-2

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Received: April 1, 2021
Peer-review started: April 1, 2021
First decision: June 17, 2021
Revised: June 27, 2021
Accepted: September 22, 2021
Article in press: September 22, 2021
Published online: December 19, 2021

P-Reviewer: Mukherjee M
S-Editor: Wang LL
L-Editor: Kerr C
P-Editor: Li JH

Core Tip: The corona virus disease 2019 (COVID-19) pandemic has resulted in most nations deciding upon self-isolation and social distancing policies for their citizens to control the pandemic and reduce hospital admission. This review aimed at evaluating the effect of physical activity on mental well-being during the COVID-19 pandemic. COVID-19 may lead to cardiovascular and neurological disorders associated with inflammatory effects of viral infection affecting brain tissues, leading to nervous system damage and cognitive dysfunction, insulin sensitivity reduction, and behavioral impairments. Regular physical activities may reduce inflammatory responses, improve angiotensin-converting enzyme-2 responses, and mental well-being during self-isolation and social distancing.

Citation: Abdelbasset WK, Nambi G, Eid MM, Elkholi SM. Physical activity and mental well-being during COVID-19 pandemic. *World J Psychiatr* 2021; 11(12): 1267-1273
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1267.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1267

INTRODUCTION

The corona virus disease 2019 (COVID-19) pandemic caused by the novel coronavirus SARS-CoV-2 appeared in China in 2019[1]. The infection probably resulted from a usual assortment of animal hosts prior to zoonotic spread that affected populations worldwide and caused thousands of deaths[2]. Through a cellular membrane receptor known as angiotensin-converting enzyme-2, SARS-COV-2 influences host cells, affects lungs with insufficient oxygen supply, and accordingly may affect cardiac and brain tissues[3]. With the rapid progress of COVID-19, most nations decided upon self-isolation and social distancing policies for their citizens and residents to control the pandemic and reduce hospital admission, with a recommendation of self-isolation and social distancing to successfully control the pandemic outbreak[4].

At this time, it is important for all populations to understand the local characteristics of COVID-19 transmission and social distancing policy as the transmission of COVID-19 is predicted to occur up to 2024, and intermittent or extended social distancing may be continued to 2022 and will cause major lifestyle changes among people worldwide[5]. Therefore, it is doubtful during these policies that individuals can continue their sedentary behaviors to maintain their healthy condition[6]. Government policies of social isolation and distancing during the COVID-19 pandemic can increase disturbance of mental health, including anxiety and depression[7]. Figure 1 presents the negative effects of the COVID-19 pandemic on physical activity and mental health.

Nutritional deprivation may affect cognitive status and lead to mood disorders[8]. Poor physical activity levels during COVID-19 quarantine can also lead to sedentary behaviors that could lead to the development of chronic cardiovascular, metabolic and mood disorders[9,10]. Several studies have reported that regular physical activity and exercise training are considered effective nonpharmacological interventions in several chronic disorders[9].

MENTAL HEALTH AND COMMUNITY

Generally, the development and prevalence of mental health impairments are associated with social and physical determinants[11]. Community service integration may promote awareness of mental well-being, reduce discrimination and stigma, support social recovery, and prevent mental dysfunction[12,13].

International guidelines accentuate community care for mental well-being and the World Health Organization also has suggested stipulations of integrated and comprehensive social care for mental well-being, including prevention and interventional protocols in the community incorporating the perceptions of families and service providers[14]. It is reported that individuals with psychological impairment should be encouraged to live without assistance among populations[15].

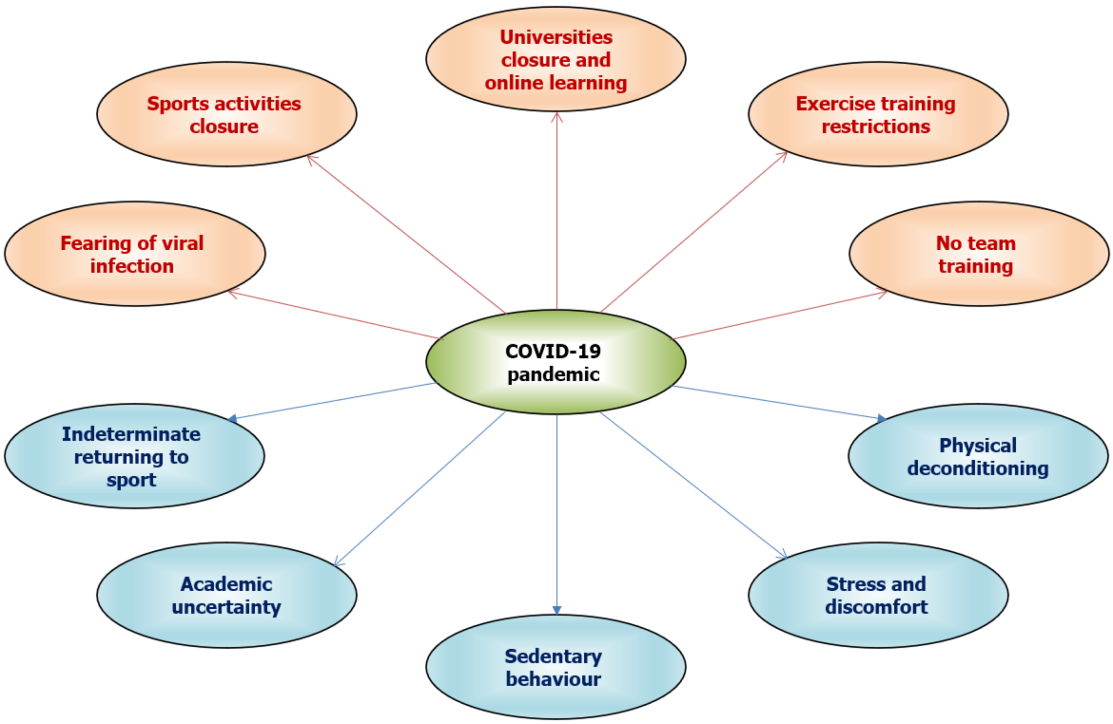


Figure 1 Negative effects of COVID-19 pandemic on physical and mental well-being.

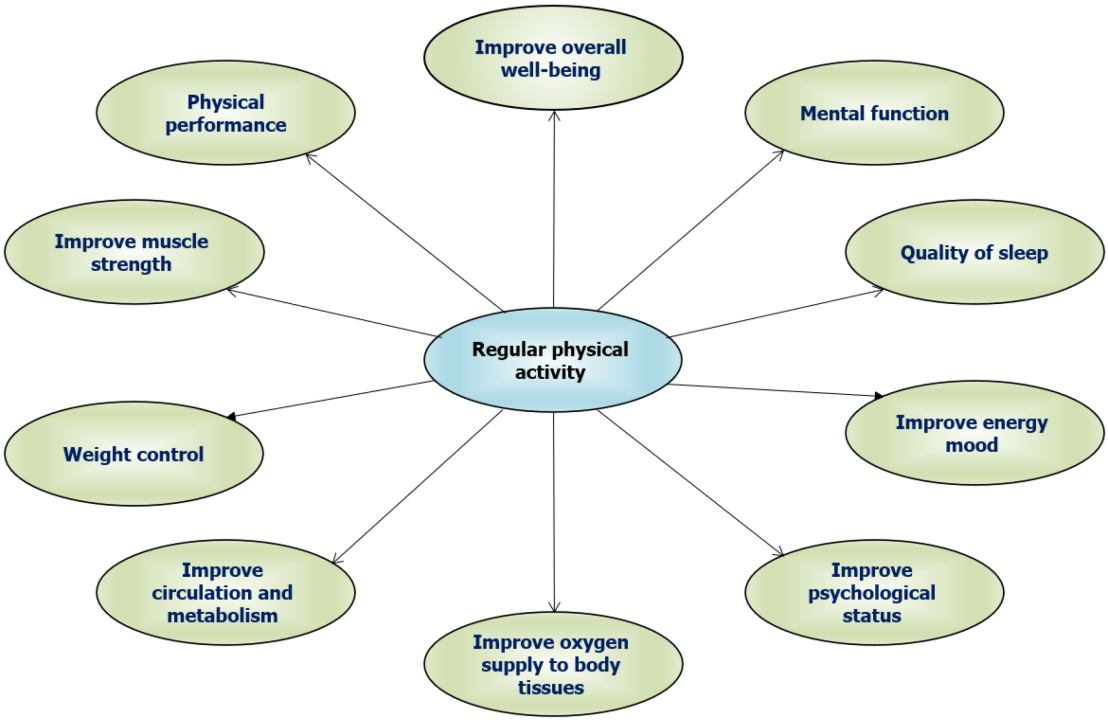


Figure 2 Positive effects of regular physical activity on physical and mental well-being.

NEUROLOGICAL MANIFESTATIONS RELATED TO COVID-19

Brain tissues may be affected by viral infection due to infected nerve cells through infected vascular endothelium, or leukocyte migration into the brain circulation[16]. Although headache and anosmia are the major prevalent neurological disorders related to COVID-19, neurophysiological impairments have been documented, including encephalopathy, seizures, consciousness impairment, and stroke[17,18].

Table 1 Physical activity and mental health during COVID-19 pandemic

Refs	Measures	Findings and recommendations
Wright *et al* [32], 2021	Incidence of fear, physical activity, and mental well-being indicators questionnaires	Physical activity may improve mental well-being and protect against the undesirable impacts of COVID-19. Regular physical activities should be encouraged to improve mental well-being during COVID-19 pandemic.
Xiao *et al* [33], 2021	Lifestyle and home environment, physical and mental well-being, and occupational environment questionnaires	Significant reduction in physical and mental well-being including impaired physical activity, increased junk food intake, and absence of coworker communications
Faulkner *et al* [34], 2021	Short form of IPAQ, WHO-5 well-being index, and depression, anxiety and stress scale-9	Negative changes in physical activity before COVID-19 containment policies presented poor mental well-being, while positive physical activity behavior showed better mental well-being
Meyer *et al* [35], 2020	Self-reported physical activity, anxiety and depression status, social connection, loneliness, and stress	Adherence to physical activity contributions and restrictive screening time during unexpected societal alterations may alleviate the consequences of mental well-being
Carriedo *et al* [36], 2020	International Physical activity questionnaire (IPAQ), 6-item self-report scale of depression symptoms, Connor-Davidson CD-RISC resilience scale, and positive and negative affect schedule	Regular moderate or vigorous physical activity provide positive resilience and reduce depression symptoms during COVID-19 quarantine
Maugeri *et al* [37], 2020	IPAQ and psychological general well-being index	Reduced physical activity have a greatly undesirable effects on psychological status and mental well-being. Adherence to a regular physical activity program is the main approach for improving physical and mental well-being during COVID-19 confinement.
López-Bueno *et al*[38], 2020	Short form of physical activity vital sign and single-item question for mood and anxiety	Adherence to regular physical activities associated with better mood and lower anxiety with WHO recommendations during COVID-19 quarantine
Duncan *et al* [39], 2020	Online survey on perceived changes in physical activity due to COVID-19 mitigation and mental well-being using 10-item perceived stress scale and 6-item anxiety subscale	COVID-19 mitigation policies may affect physical activity and mental well-being. Participants with reduced physical activity levels showed higher anxiety and stress levels.
Jacob *et al* [40], 2020	Self-reported physical activity questionnaire, Beck anxiety and depression inventories, and 7-item short Warwick-Edinburgh mental well-being scale	During COVID-19 social distancing, participants adherent to vigorous and moderate physical activity showed better mental well-being

COVID-19: Corona virus disease 2019.

It was reported that approximately 36% of COVID-19 patients suffered from neurological symptoms such as impaired consciousness and cerebrovascular disorders associated with inflammatory effects of viral infection[19]. This inflammation may affect the brain tissues leading to damage of the nervous system and cognitive dysfunction, insulin sensitivity reduction, and behavioral impairments[20]. Also, these inflammatory reactions associated with viral infection may develop primitive neurological manifestations[21].

Due to impaired neural plasticity, the initial fatality of nerve cells, and disturbed neurotransmitter production, psychoses, impaired memory, and post-traumatic stress disorders may occur with COVID-19[22]. In addition, angiotensin-converting enzyme (ACE)-2 is expressed with COVID-19 in several brain areas, such as the olfactory system, striatum, and cortex, and on various types of nerve cells such as astrocytes, microglia, neurons, and oligodendrocytes[23]. The primary projected mechanism that affects the function of the nervous system is ACE-2 activation associated with COVID-19 through augmentation of inflammatory responses[20,23].

PHYSICAL ACTIVITY AND MENTAL HEALTH

A recent cross-sectional study found that individuals who conducted a regular physical exercise for one month had good life satisfaction during quarantine, while the individuals who stayed at home and without physical exercise suffered from poor health conditions[24]. It was also reported that isolation and social distancing related to COVID-19 led to a greater incidence of anxiety and depression[25]. Accordingly, these reports suggest that individuals who conducted physical exercise during COVID-19 should be regularly observed as they may be particularly irritated by self-isolation. Therefore, exercise training for a long time does not indicate good mental well-being, but it may be a predictor of developing mood disorders[25].

It can be assumed that overtraining or prolonged exercise training may lead to pessimistic health conditions such as mood disorders[20]. The quarantine associated with COVID-19 may increase the development of a sedentary lifestyle among different populations including adolescents[26]. Regular exercise training improves immune function, lowers the severity of symptoms, and reduces the mortality rate in individuals exposed to viral infection[10]. Conducting physical activity or sports during the COVID-19 pandemic may provide a complementary and alternative treatment to develop mental well-being[27].

It is documented that COVID-19 may be associated with neurotropism, neuroinvasion, and neuroinflammation that could clearly affect the outcomes of mental well-being including acute myelitis, cerebrovascular disorders, encephalitis, and encephalopathy[28]. Several exercise training programs and different laboratory investigations should be conducted to assess the influence of exercise training on COVID-19 and how it prevents disturbances of mental well-being. Regrettably, studies that suggest or explain the ideal exercise protocol conducted during the COVID-19 pandemic and its influence on mental and cardiovascular well-being are limited, and therefore the relationship between exercise training, cardiovascular function, and mental well-being should be investigated.

Anxiety and depression are the most frequent mental disorders, with varied incidence rates among different ages, including adults, adolescents, children, and particularly aged individuals[29]. It is reported that anxiety and depression may lead to negative effects on various quality of life domains, such as being physically inactive [30]. The pathophysiology of anxiety and depression is still not clearly explained, and an abundance of biomarkers have been recommended to identify the sequences and development of mental disorders[30,31].

Recent studies have proved that adherence to physical activities and exercise training programs during COVID-19 quarantine is associated with better mental health and lower anxiety and depression levels. However, poor physical activity levels are associated with higher levels of anxiety and depression in addition to poor mental health and well-being[32-40] (Table 1).

Exercise training and physical activity have been suggested as nonpharmacological interventions to eliminate the complications associated with self-isolation and social distancing during the COVID-19 pandemic [27]. The effects of different exercise programs are not being clearly investigated during the COVID-19 pandemic. Physical activity may improve mental well-being and protect against the undesirable impacts of COVID-19. Regular physical activities should be encouraged to improve mental well-being during the COVID-19 pandemic[32-40]. Figure 2 shows the positive effects of regular physical activity on physical and mental well-being.

CONCLUSION

The COVID-19 pandemic may lead to augmented levels of ACE-2 that led to cardiovascular and neurological disorders associated with inflammatory effects of viral infection, affecting the brain tissues and leading to damage to the nervous system and cognitive dysfunction, insulin sensitivity reduction, and behavioral impairments. Anxiety and depression may lead to negative effects on various quality of life domains, such as being physically inactive. Regular physical activities may reduce inflammatory responses, improve ACE-2 responses and mental well-being during self-isolation and social distancing related to the COVID-19 pandemic. Further studies should be conducted to assess the different intensities of physical activities on cardiovascular function, and mental well-being during the COVID-19 pandemic.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1274-1287

DOI: 10.5498/wjp.v11.i12.1274

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Basic Study

Differential aberrant connectivity of precuneus and anterior insula may underpin the diagnosis of schizophrenia and mood disorders

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Author contributions: Kandilarova S and Stoyanov D designed and coordinated the study; Kandilarova S, Aryutova K, Paunova R and Stoyanova K performed the experiments; Kandilarova S and Paunova R acquired and analyzed the data; Aryutova K and Paunova R interpreted the data; Aryutova K wrote the original draft; Aryutova K prepared the visualization; Maes MH, Kandilarova S and Stoyanov D reviewed and edited the original draft; all authors approved the final version of the article.

Institutional review board statement: The Ethics Committee at Medical University of Plovdiv has approved the protocol of the study on 29 May 2015 (ID: P-369/29.05.2015).

Informed consent statement: The informed consent statement was waived.

Conflict-of-interest statement:

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Abstract

BACKGROUND

Over the past decade, resting-state functional magnetic resonance imaging (rs-fMRI) has concentrated on brain networks such as the default mode network (DMN), the salience network (SN), and the central executive network (CEN), allowing for a better understanding of cognitive deficits observed in mental disorders, as well as other characteristic psychopathological phenomena such as thought and behavior disorganization.

AIM

To investigate differential patterns of effective connectivity across distributed brain networks involved in schizophrenia (SCH) and mood disorders.

METHODS

The sample comprised 58 patients with either paranoid syndrome in the context of SCH (n = 26) or depressive syndrome (Ds) (n = 32), in the context of major depressive disorder or bipolar disorder. The methods used include rs-fMRI and subsequent dynamic causal modeling to determine the direction and strength of connections to and from various nodes in the DMN, SN and CEN.

RESULTS

A significant excitatory connection from the dorsal anterior cingulate cortex to the anterior insula (aI) was observed in the SCH patient group, whereas inhibitory connections from the precuneus to the ventrolateral prefrontal cortex and from the aI to the precuneus were observed in the Ds group.

CONCLUSION

Authors declare no conflict of interest.

Data sharing statement: Data are available to share on demand.

Country/Territory of origin: Bulgaria

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

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Received: April 14, 2021
Peer-review started: April 14, 2021
First decision: June 5, 2021
Revised: June 15, 2021
Accepted: August 31, 2021
Article in press: August 31, 2021
Published online: December 19, 2021

P-Reviewer: Kaur M, Tung TH, Wang DW
S-Editor: Fan JR
L-Editor: Kerr C
P-Editor: Guo X

The results delineate specific patterns associated with SCH and Ds and offer a better explanation of the underlying mechanisms of these disorders, and inform differential diagnosis and precise treatment targeting.

Key Words: Schizophrenia; Major depressive disorder; Bipolar disorder; Resting-state functional magnetic resonance imaging; effective connectivity; precuneus; insula; default mode network; salience network

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Core Tip: The present study reports a significant excitatory connection from the anterior cingulate cortex to the anterior insula (aI) that was observed in the schizophrenia patient group, whereas inhibitory connections from the precuneus (Pc) to the ventrolateral prefrontal cortex and from aI to Pc were observed in the major depressive episode group. The results delineate specific aberration patterns which correspond to the clinical presentations of the nosological units and can further contribute to a better explanation of the underlying mechanisms of these disorders as well as to inform differential diagnosis and precise treatment targeting.

Citation: Aryutova K, Paunova R, Kandilarova S, Stoyanova K, Maes MH, Stoyanov D. Differential aberrant connectivity of precuneus and anterior insula may underpin the diagnosis of schizophrenia and mood disorders. *World J Psychiatr* 2021; 11(12): 1274-1287
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1274.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1274

INTRODUCTION

Schizophrenia (SCH) is one of the most devastating and socially important diseases, as well as one of the most poorly understood mental conditions that affects people typically in late adolescence/early adulthood and leads to a functional decline in the personal, social and economic aspects of those affected[1]. Although psychotic symptoms, such as delusions and hallucinations, are the most commonly associated behavioral manifestations of SCH, it is primarily a cognitive disorder[2] with an established specific disability profile in terms of cognition and psychosocial dysfunction, and some authors recommend using that as a special differential diagnostic criterion in existing diagnostic instruments[3-5]. However, mood disorders are also often accompanied by serious cognitive deficits[6,7] and these deficits often persist well after symptomatic relief. Furthermore, the most severe cognitive deficits in patients with depressive syndrome (Ds) have been identified in the same cognitive domains as those seen in SCH spectrum disorders, including concentration, memory and executive functions[7-9].

Unlike other diseases, mental illnesses are classified into diagnostic categories based on top-down, phenomenologically derived criteria. The clinical manifestations of psychiatric disorders are not only multifaceted but also characterized by a high incidence of symptom overlap[10]. As a result of their poor biological validity concerning their etiology due to the limited knowledge about the exact pathological processes, the assessment methods in psychiatry exist outside of the traditional medical framework[11,12]. The contemporary gold standard, represented by the Diagnostic and Statistical Manual of Mental Disorders 5th edition[13] and the International Classification of Diseases X division[14] taxonomies, appears to have a lot of inconsistencies[12]. Thus, the use of those manuals leads to the conclusion that mental illnesses often have high rates of comorbidity, heterogeneity, and presence of intermediate cases[12]. For example, studies show that around half of the SCH cases exhibit symptoms that can be fitted into the category of a Ds[15,16]. In contrast to the presence of a single mental disorder, the presence of two or more mental illnesses is related to increased severity, inadequate pharmacological treatment response, and a substantial suicide risk[17]. This, along with a lack of comprehensive knowledge about the neural and molecular mechanisms that underpin behavioral deviations, explains the therapeutic failures in SCH and mood disorders. All the above-mentioned

inconsistencies highlight the imperative need to identify diagnostic biomarkers in psychiatry.

Functional magnetic resonance imaging (fMRI) in psychiatric research is often used to collect signals from brain regions indicating blood oxygen level dependent changes in response to cognitive tasks [task-related fMRI (tr-fMRI)]. Those kinds of studies suggest impaired brain activity during cognitive load involving language, memory, and concentration in patients with mental illness[18-21].

In contrast, resting-state fMRI (rs-fMRI) is a popular instrument for macroscale functional connectomics that can localize low-frequency differences in random brain functions representing interindividual variations in brain activity and mind–brain interactions found in different psychiatric disorders[22]. Over the past decade, rs-fMRI has concentrated on brain networks such as the default mode network (DMN), the salience network (SN), and the central executive network (CEN), allowing for a better understanding of cognitive deficits observed in SCH and mood disorders, as well as other characteristic SCH phenomena such as thought and behavior disorganization [23].

In a previous study[24], we investigated the rs-fMRI effective connectivity in SCH patients with paranoid syndrome and patients with mood disorders with Ds. In addition, in the same sample, we performed tr-fMRI of the von Zerssen's Paranoid-Depressive Self-Assessment Scale[25], which consists of paranoid-specific, depressive-specific and neutral items. An example of a paranoid-specific item on the scale is "Other people constantly follow and control me", and an example of a depressive-specific item is "I often feel simply miserable". The results from tr-fMRI show that the areas that are activated in SCH patients during paranoid-specific items, including the precuneus (Pc) and the posterior cingulate cortex are parts of the DMN, whereas the results for the Ds sample in the same study did not yield any significant clusters of activations. The results from the resting state effective connectivity, however, informed an inhibitory connection from the prefrontal cortex (PFC) to the anterior insula (aI) in the SCH group, which was completely absent in the Ds group. These data led us to assume that disrupted connectivity from the PFC⇒aI at rest may contribute to impaired cognitive functions, behavioral disorganization, and functional disability in people suffering from SCH[26]. Furthermore, the observed DMN activation during the task might be indirect evidence of the inhibitory connection from the PFC⇒aI at rest, which could interfere with the balancing function of the SN as a dynamic switch between the DMN and CEN[24,27].

As the Pc is an integrated element in the DMN and the aI is a central hub in the SN, we hypothesize that functional disruptions in those regions are linked to behavioral abnormalities and cognitive deficits in psychotic disorders. The DMN is characterized by a high baseline firing rate at rest and deactivation at cognitive tasks onset[28]. As the DMN is described as a network that normally activates at rest[29], little is known about the exact mechanisms by which the DMN is activated in SCH patients during the performance of a task. Therefore, our goal was to identify specific patterns in the resting-state effective connectivity of the SN and DMN in the SCH and Ds groups that could explain the behavioral deficits observed in both the paranoid and Ds groups, as well as to test whether these deficits share common or distinct neuropatho-physiological patterns.

We decided to test whether at rest, when patients are instructed not to think about anything specific, there was altered connectivity between the components of the SN and DMN, comparing two disease units – SCH (paranoid syndrome) *versus* mood disorders (Ds).

Hence, the present study was conducted to delineate the effective connectivity patterns at rest with a prior hypothesis that the SN in SCH must have a fundamentally impaired connectivity, which prevents the switching between DMN and CEN, thereby interfering with their basic functions. Our motivation to conduct such a comparative study came from the aforementioned discrepancies, which arise from the lack of biological validity of available diagnostic tools, which ultimately leads to inaccurate diagnosis or high comorbidity in psychotic and affective disorders. By proving neurobiological markers to distinguish the two disorders, we aimed to expand knowledge about their etiology and incorporate it into clinical practice, ultimately optimizing diagnosis and prognosis, and thus choosing the right treatment for these severe mental illnesses.

MATERIALS AND METHODS

Participants

For the current study, we recruited 58 patients, namely 26 with a paranoid syndrome –in the context of SCH (mean age 39.2 ± 13.2 years, 13 male) and 32 with Ds (mean age 42.9 ± 11.7 years, 10 male) – in the context of major depressive disorder (MDD) (n = 14, mean age 42.4 ± 12 years, 5 male), or bipolar disorder (BD) (n = 18, mean age 43.3 ± 11.8 years, 5 male) – according to the diagnostic criteria of DSM IV Text Revision[30]. The assessment of the participants was performed by experienced psychiatrists (DS, SK and KA) using the general clinical interview[31], the structured Mini-International Neuropsychiatric Interview (M.I.N.I. 6.0)[32], and clinical global impression scale[33]. The positive and negative syndrome scale[34] was chosen for the assessment of the SCH group. A minimum rating of 3 on P1 (delusions) and/or P6 (suspiciousness) was set to secure a reasonable severity of the episode. The severity of the depressive episode was assessed using the Montgomery–Åsberg Depression Rating Scale[35]. A cut-off value of 20 was chosen, which is considered to constitute a DS of moderate severity. Both clinical groups were on stable medication for at least 14 d.

The requirements for participation were the following: age > 18 and < 65 years; lack of metal implants (*e.g.*, pacemaker); absence of comorbidity with other psychiatric disorders (substance use disorders, anxiety disorders, *etc.*); and absence of severe neurological disorders or traumatic brain injury with loss of consciousness. Psychiatric history was further considered as a source of information to supplement the exclusion criteria. Each of the patients provided a written informed consent complying with the Declaration of Helsinki. The protocol of the study was approved by the University's Ethics Committee (ID: P-369/29.05.2015).

Image acquisition

Subjects were scanned on a 3T MRI system (GE Discovery 750w) and the protocol included the following sequences: (1) high-resolution structural scan (Sag 3D T1 FSPGR, slice thickness 1 mm, matrix 256 × 256, relaxation time (TR) 7.2 ms, echo time (TE) 2.3 ms, flip angle 12; and (2) resting-state functional scan-2D echo planar imaging (EPI), with slice thickness 3 mm, matrix 64 × 64, TR 2000 ms, TE 30 ms, 36 slices, flip angle 90, a total of 192 volumes. Before the EPI sequence, subjects were instructed to remain as still as possible with eyes closed and not to think of anything.

Resting-state data analysis

The SPM 12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/) software running on MATLAB R2020b for Windows was used to perform data analysis. During the preprocessing of the EP images, they were realigned, co-registered with the structural scans, normalized to Montreal Neurological Institute (MNI) space, and smoothed with a 6-mm full-width-at-half-maximum Gaussian kernel.

First-level resting-state analysis was conducted using a general linear model applied to the time series. Regions of interest (ROIs) were predefined based on their involvement in the SN and the DNM with 6-mm radius spheres. The ROIs with their MNI coordinates are presented in Table 1.

These five ROIs were subjected to spectral dynamic causal modeling (spDCM). We used a completely connected model, which meant that each node was linked to the others. A spectral DCM, in contrast to a stochastic DCM, measures effective connectivity from the cross spectra of changes in neuronal states rather than directly from their time courses[36]. Furthermore, using the parametric empirical bayes method introduced in SPM12, the individual spDCM models were jointly estimated. Finally, the estimated spDCM models were used to extract connectivity strengths (A-matrix) for further statistical analysis in SPSS.

Statistical analysis

Statistical analysis of the demographic and clinical characteristics of the participants, as well as of the connectivity strengths of the spDCM model were performed using SPSS for Windows 22.0. The level of significance was set to $P < 0.05$, two-tailed, for all tests. Student's t test was used for continuous variables and the χ^2 test for categorical variables. The normality of distribution of the coupling values was tested with the Shapiro–Wilk test and the significance of all tests was set at 0.05.

Table 1 Regions of interest with their Montreal Neurological Institute coordinates

Region of interest	X	Y	Z	Brodmann area
DLPFC (left)	-28	46	26	46
VLPFC–opercular part of the IFG (left)	-41	19	41	44
dACC (left)	0	32	26	24
aI (left)	-36	14	-4	48
Pc (left)	-10	-54	30	23

DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; IFG: Inferior frontal gyrus; dACC: Dorsal Anterior cingulate cortex; AI: Anterior insula; Pc: Precuneus; X, Y, Z: Montreal Neurological Institute coordinates.

RESULTS

Demographic and clinical characteristics

There were no significant differences in age, sex, age of onset, episode duration, and education level between SCH and Ds patients. The clinical characteristics of the whole patient sample are given in detail in Table 2. The two subgroups of Ds (bipolar and unipolar) did not differ significantly in their demographic or clinical variables (Table 3).

Resting-state results

We performed the analysis as described above and received various connections between the ROIs. The significant connections are described below within the different groups of patients and between them.

Resting-state effective connectivity in patients with Ds: The coupling connectivity strengths that significantly differed from zero in the group of patients with Ds are presented in Table 4 and Figure 1. There were 15 significant both inhibitory and excitatory connections mainly engaging the prefrontal and parietal regions.

Resting-state effective connectivity in SCH patients: The results from the one-sample *t* test in the SCH group yielded seven connections that were significantly different from zero. These connections were presented mostly by SN regions and the Pc, as well as self-inhibition of the dorsal anterior cingulate cortex (dACC). The ventrolateral prefrontal cortex (VLPFC) did not present in any of the significant connections. A detailed description of the results is given in Table 5 and Figure 2.

Differences in the resting-state effective connectivity between SCH and Ds patients: To explore the differences between the two groups, independent samples *t* tests comparing the mean connectivity strengths were performed. The coupling strengths of the connection from the Pc to VLPFC and from the aI to the Pc, both inhibitory connections, were present in the Ds group but absent in the SCH group. In the SCH patients, a significant excitatory connection from the dACC to aI was present that was absent in the Ds group (Figure 3).

The findings of this study suggest that physicians treating patients with SCH and Ds should communicate with their patients that their illness is characterized by alterations in brain connectome data, which in part may explain their symptoms.

DISCUSSION

Our analysis of the rs-fMRI data demonstrated that, in the patients with Ds, significant excitatory influence was exerted dorsolateral prefrontal cortex (DLPFC)⇒Pc, DLPFC⇒dACC, dACC⇒Pc, dACC⇒DLPFC and VLPFC⇒Pc, while inhibitory influences were exerted Pc⇒dACC, Pc⇒VLPFC, Pc⇒DLPFC, aI⇒Pc, aI⇒VLPFC, and VLPFC⇒dACC and self-inhibition of the VLPFC, dACC and aI.

In the SCH patients, significant effective connectivity, that is, causal interaction in terms of excitatory influence, was exerted dACC⇒aI, dACC⇒DLPFC and DLPFC⇒aI, whereas inhibitory influences were exerted Pc⇒dACC, Pc⇒DLPFC and aI⇒dACC, and self-inhibitory influence of the dACC. The VLPFC in the SCH group did not participate in any interactions with the other ROIs.

Table 2 Demographic and clinical characteristics of all participants

	SCH patients (*n* = 26)	Ds patients (*n* = 32)	*P* value
Age (mean ± SD)	39.2 ± 13.2	42.9 ± 11.7	0.448[1]
Sex (M/F)	13/13	10/22	0.115[2]
Education (years)	13.6 ± 3.1	13.5 ± 3.2	0.871[1]
Age at onset (years)	25.8 ± 8	32.1 ± 11.8	0.060[1]
Episode duration (weeks)	19.6 ± 28	13.7 ± 16.8	0.159[1]

[1]Independent samples *t* test.
[2]χ^2 test, $P < 0.05$.
SCH: Schizophrenia; Ds: Depressive syndrome; SD: Standard deviation.

Table 3 Demographic and clinical characteristics of the two depressive syndrome subgroups

	MDD patients (*n* = 14)	BD patients (*n* = 18)	*P* value
Age (mean ± SD)	42.4 ± 12	43.3 ± 11.8	0.286[1]
Sex (M/F)	5/9	5/13	0.712[2]
Education (years ± SD)	14.6 ± 3.8	12.8 ± 2.6	0.197[1]
Age at onset (years)	30 ± 12	31.5 ± 12	0.734[1]
Episode duration (weeks)	8.8 ± 9.3	17 ± 20	0.197[1]

[1]Independent samples *t* test.
[2]χ^2 test, $P < 0.05$.
MDD: Major depressive disorder; BD: Bipolar disorder; SD: Standard deviation.

However, the main findings from the comparison between the two groups can be summarized as follows: (1) In the Ds group, during rs-fMRI, there was strong involvement of the Pc, which is the central hub of the DMN. There was an inhibitory connection from the aI to the Pc and from the Pc to the PFC; and (2) In the SCH group, during rs-fMRI, there was no DMN activity but instead, there was an excitatory connection from the anterior cingulate cortex to the aI regions that compose the SN.

Concerning the significant deviations observed in the patients with Ds, the following can be discussed. The Pc is a central node of the DMN[37] that becomes more involved during rest when the mind is in a task-free state[38] and its altered function has long been thought to be a neuronal substrate for depression[39]. It plays an important role in the integration of mental processing through its participation in cognitive control functions including visual imagery, episodic memory, and self-directed processes. The observed inhibitory influence from Pc⇒PFC could be related to increased internal ruminating thoughts that are a characteristic trait in patients suffering from Ds[40].

The VLPFC is a component of the PFC that is situated on the inferior frontal gyrus (IFG) that belongs to Brodmann's field 44, which we included as an ROI in our study. Our results demonstrate that, in the Ds group, the DMN exerted an inhibitory influence upon the PFC (particularly the IFG). Studies on the therapeutic effect of ketamine, which is one of the most effective known treatments in the management of suicidality and self-injurious behavior[41,42], show that ketamine normalizes alterations in this area, namely on its opercular part (which was examined in the current study – Broadman's field 44)[43].

The rapid effect of ketamine, which is most likely due to its action on the IFG, conjoined with the lack of consistency in the improvement of the condition, indicates that the disturbances in the IFG might be secondary. Our results suggest a model in which the Pc is the primary component responsible for the secondary deficiencies in the IFG function. We hypothesize that the effect of ketamine may be prolonged by combining it with a therapeutic method that acts directly on the Pc, which would ultimately lead to a normalization of the altered effective connectivity (inhibition of Pc ⇒IFG) and thus an improvement in IFG function. Such a suitable therapeutic tool could be the repetitive transcranial magnetic stimulation (rTMS)[10], whose effects can

Table 4 Connections significantly different from zero in the depressive syndrome group

Connections	Mean	*P* value
dACC→DLPFC	0.146	0.029[a]
Pc→DLPFC	-0.239	0.002[b]
VLPFC⊃	-0.185	0.002[b]
dACC→VLPFC	0.180	0[c]
aI→VLPFC	-0.250	0.002[b]
Pc→VLPFC	-0.177	0.007[b]
DLPFC→dACC	0.212	0.004[b]
VLPFC→dACC	-0.181	0.02[a]
dACC⊃	-0.160	0.007[b]
Pc→dACC	-0.228	0.006[b]
aI⊃	-0.216	0.003[b]
DLPFC→Pc	0.090	0.047[a]
VLPFC→Pc	0.133	0.029[a]
dACC→Pc	0.090	0.049[a]
aI→Pc	-0.284	0[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
⊃: Self-inhibitory connection; DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; IFG: Inferior frontal gyrus; dACC: Dorsal anterior cingulate cortex; AI: Anterior insula; Pc: Precuneus.

Table 5 Connections significantly different from zero in the schizophrenia group

Connections	Mean	*P* value
dACC→DLPFC	0.172	0.004[b]
Pc→DLPFC	-0.384	0.001[b]
dACC⊃	-0.189	0.009[b]
aI→dACC	-0.303	0.013[a]
Pc→dACC	-0.366	0.001[b]
DLPFC→aI	0.110	0.039[a]
dACC→aI	0.126	0.026[a]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
⊃: Self inhibitory connection; DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; dACC: Dorsal Anterior cingulate cortex; aI: Anterior insula; Pc: Precuneus.

be detected not only in the targeted stimulation area but also in other distant areas of the brain that are functionally relevant and occur on existing neural networks[44].

In individuals with Ds, cognitive and emotional aspects linked to the insula are impaired, suggesting that the insula dysfunction may be at the core of the disease's clinical manifestations[45]. Activity in both the IFG and the aI is often dismissed as being relevant only to motor inhibition or orienting responses and therefore not functionally significant or cognitive. Tops and Boksem[46], however, demonstrated that IFG/aI is involved in dynamic attentional and working memory processing. The IFG/aI is also one of the regions that commonly demonstrates elevated activity related to anxiety and distress[47], which are typical features of the Ds. In addition, antide-

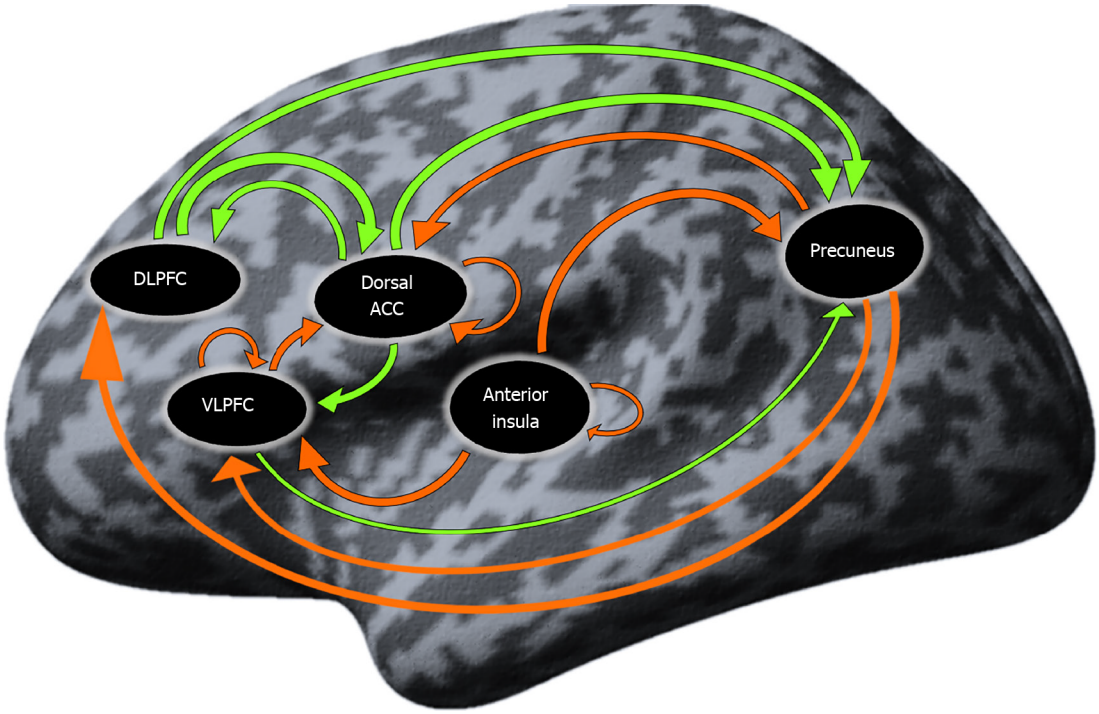


Figure 1 Connections significantly different from zero ($P < 0.05$) in the depressive syndrome group. Orange arrow: Inhibitory influence; green arrow: Excitatory influence. DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; Dorsal ACC: Dorsal anterior cingulate cortex.

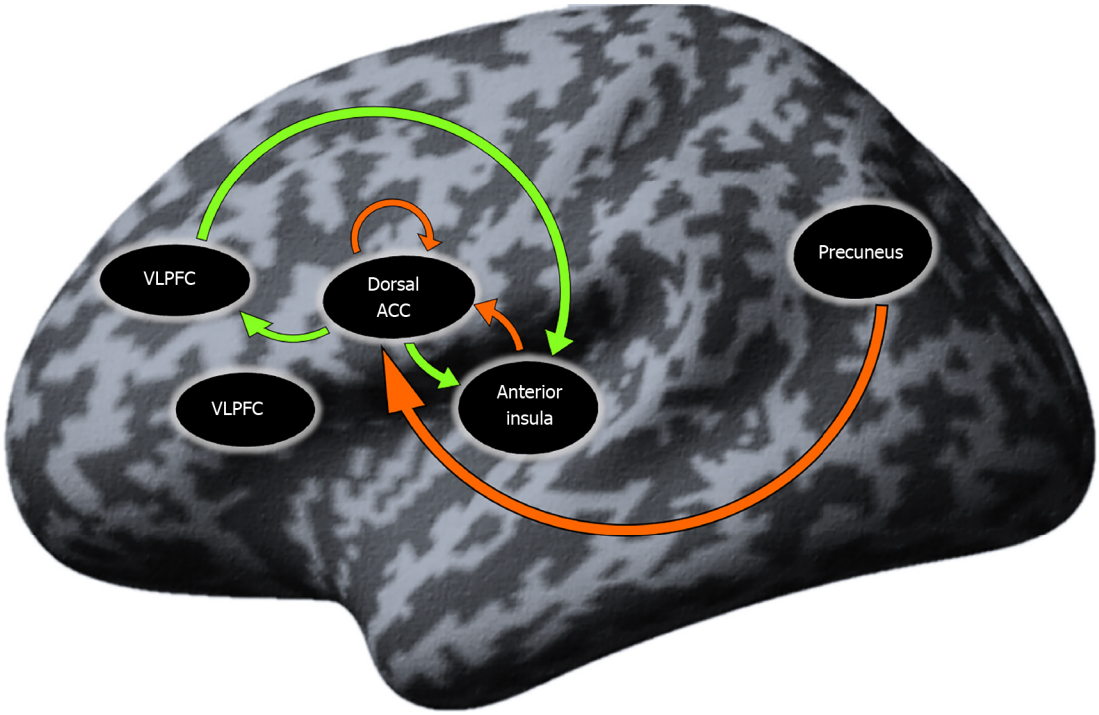


Figure 2 Connections significantly different from zero ($P < 0.05$) in the schizophrenia group. Orange arrow: Inhibitory influence; green arrow: Excitatory influence; DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; Dorsal ACC: Dorsal anterior cingulate cortex.

pressant treatment and sleep deprivation are attributed to a change in activation from the IFG/aI to the DLPFC[48]. This may be due to Ds patients' difficulty disengaging from issues and rumination, which decreases optimistic prospective and retrospective memory[49].

Analyzing our findings on patients in a depressive episode, we suggest that future research should focus deeper on examining the impaired effective connectivity between important brain regions, most notably the PFC, insula and Pc, relying on the

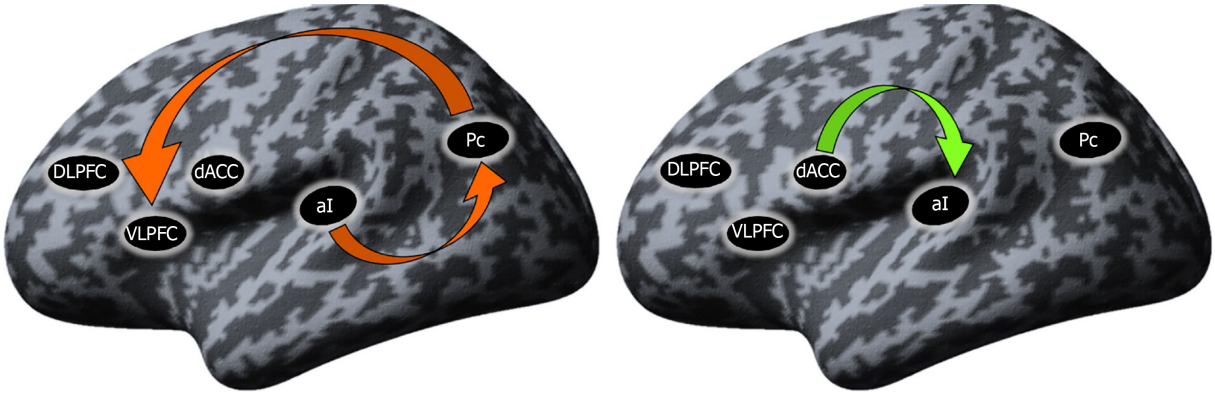


Figure 3 Connections significantly different from zero ($P < 0.05$) between the two groups. Red arrow: Inhibitory influence; green arrow: Excitatory influence; DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; dACC: Dorsal Anterior cingulate cortex; aI: Anterior insula; Pc: Precuneus.

translational approach in neuroscience aimed at incorporating the gained knowledge into clinical practice for more successful treatment options for the Ds. We hypothesize that our findings may serve in this process by combining the psychopharmacological approach, using ketamine, which is known to modulate the function of the IFG, together with a biomedical instrumental method rTMS, targeting the Pc and PFC. Such a translational therapeutic approach could lead to a lasting improvement in the condition and ultimately optimize the prognosis of the disease.

Concerning the significant deviation (excitatory connection from the dACC⇒aI) observed in the SCH group, the following findings can be discussed: The dACC is a key region involved in cognitive and emotional processing[50,51]. Brodmann's area 24 (dACC, which we examined) was associated in the past with abnormal behavioral manifestations which laid the foundation for bilateral cingulotomy psychosurgery. In such cases, neuropsychological follow-up revealed cognitive deficiency, especially in the executive functions[52]. Heilbronner and Hayden[53] suggested that the dACC is a structure specialized for representing task-state conditions that influence actions and that dACC neurons link context with strategies by combining a variety of task-relevant information to construct a representation of abstract control over decisions and actions.

The aI is an integral center for mediating dynamic interactions between large-scale brain networks engaged in externally oriented attention and self-cognition. This brain structure performs numerous cognitive, affective, and regulatory processes, including interception, emotional reactions, and empathy. The roles delegated to the insula can be conceptualized through a few simple mechanisms: bottom-up identification of salient events; shifting between other large-scale networks to promote access to attention and working memory capacity when a salient event is registered; involvement of the anterior and posterior parts to adjust the autonomic response to salient stimuli; and strong functional connectivity with the ACC[54]. The perception of both visual and auditory emotional information, pain, and subjective projections of the self are all insula-related functions that are disrupted in SCH[55]. The processing of self-representations is important for distinguishing between self-generated and external information, meaning that insula dysfunction could lead to perceptual disturbances, a prevalent symptom of SCH.

The dACC and aI are the two major components constituting the SN. In healthy individuals, the activation of SN is normally observed through a variety of cognitive tasks[54]. Its primary function is to facilitate the switching of brain connectivity between the default mode and the task-related states[56]. Disrupted synchronization between the anti-correlated networks of DMN and CEN that underlie default modes and task-related activity has been postulated as a key pathophysiological characteristic of SCH[57]. Previous research has reported reduced SN connectivity during information processing and reward prediction in SCH[58,59]. Since those are cognitively charged tasks, and in SCH the SN has reduced activity in the performance of these tasks, both the DMN and CEN may exhibit disrupted activity.

These assumptions were confirmed in our previous study[24], where we observed altered resting-state connectivity from the PFC⇒aI and task-related activations in the Pc in patients with SCH, indicative of the involvement of neural networks such as the SN and the DMN and their abnormal interactions with each other in SCH etiopathogenesis. Other neuroimaging studies in SCH also reported evidence of reduced

inhibition of the DMN during task-related paradigms[60]. We suggested that the inhibitory frontoinsular connection at rest leads to disruption of the salience processing due to the insular dysfunction as a result of its failure as a dynamic switch between the DMN and CEN. As a result, the DMN stays active during tasks and the CEN does not manage to activate at all, which could explain the cognitive deficits observed in SCH individuals reflecting as a serious impact on their functioning in professional and social aspects.

The current data support this hypothesis, as the resting-state excitatory connection observed between SN's main components – dACC⇒aI – leads to hyperactivity of the SN and ultimately to a salient perception of reality through excessive engagement with indifferent stimuli, which explains the abnormal self-referential thinking that is a characteristic trait of SCH. It appears that inaccurate evaluation of stimuli that would usually be deemed irrelevant seems to be the source of abnormal salience processing in individuals with SCH psychoses. As a result, subthreshold stimuli become excessively attention-getting, which is referred to as aberrant salience by Kapur[61] and proximal salience by Palaniyappan and Liddle[55].

According to Kapur, the central hyperdopaminergic activity causes unwarranted salience to events that would not typically be considered as relevant, resulting in a pathologically exaggerated feeling of the significance of ordinary experiences, perceptual distortions, and delusional causal conclusions. Palaniyappan broadened Kapur's idea of aberrant salience by introducing the concept of proximal salience, with a hypothesis regarding the role of the aI in salience processing to include not just hallucinations and delusions associated with psychosis, but also the debilitating disturbances of cognition and volition associated with chronic SCH. With our current study, we manage to confirm this hypothesis as our finding (excitatory influence of dACC⇒aI) suggests that schizophrenic patients stay in a resting state of aberrant salience. This process may be relevant for the onset of psychotic symptoms, whereby hallucinations are a direct consequence of the aberrant salience[61] of internal representations, and delusions are a cognitive attempt to make sense of these aberrantly salient perceptions and further with the progression of the illness the incorrectly assigned proximal salience[55] produces not only the perceptual and cognitive disturbances of acute psychosis but also the symptoms of behavioral disorganization, *via* disturbed information processing and goalsetting.

In summary, the results of our study help to understand SCH as a behavioral disorder caused by disintegration across the key brain networks. The abnormal hyperconnectivity of the SN during rest, interfering with its dynamic switch function could explain the inability of the DMN's components to activate during rest and to deactivate during cognitive load[24]. Our prior hypothesis that the SN in SCH must have a fundamentally impaired connectivity, which prevents the switching between DMN and CEN, thereby interfering with their basic functions, was confirmed by the present study. We suggest that our findings could help both in the biological understanding of the etiology of SCH and in the development and improvement of the therapeutic approach. We visualize a future where translational neuroscience would ultimately integrate psychopathology, psychopharmacology, instrumental methods, and even neurosurgical techniques to restore the brain imbalances by modulating the altered connectivity in the brains of people suffering from SCH[10].

There were several limitations to our study, which need to be considered. First, our study sample was small and there was diagnostic heterogeneity in the Ds group consisting of both patients with MDD and BD, since our comparison is on a syndrome, not a categorical level. Moreover, all the patients were undergoing psychopharmacological treatment, which may be a confounding factor for the determined intraconnectome signatures. An important future aspect in this area may be a study of the longitudinal supervenience between the pretherapeutic and post-therapeutic resting-state signatures across the whole syndromic spectrum including depression–mania–psychosis.

Therefore, even though our data confirm previous studies of dysconnectivity in schizophrenic psychosis, such a model requires additional testing with a larger sample of patients using various imaging tools. Furthermore, the interdisciplinary translational approach in neuroscience can be applied by combining different scientific disciplines such as psychopharmacology, psychopathology, and functional neuroimaging. A suitable tool seems to be the pharmaco-fMRI, which could provide additional insights about the complex mechanisms of interactions between the key brain networks by studying the distribution of various molecules in and between nodes that compose the SN, DMN and CEN.

CONCLUSION

We managed to deliver evidence that despite the clinical overlaps, there are objective neuroimaging signatures of disease that can fundamentally distinguish SCH and mood disorders. We propose a model in which the behavioral deviations observed in the Ds group are due to abnormal inhibitory connections in the resting state between nodes of the DMN and SN with the PFC, while in the SCH group there is a hyperconnectivity of the SN, leading to the perception of indifferent internal stimuli as particularly significant. The resting state of aberrant salience observed in the SCH group has the potential to explain the psychotic symptoms, where hallucinations are an attempt to comprehend the abnormal internal salient stimuli, and delusions are a secondary cognitive phenomenon through which the patient explains these abnormal perceptions. In addition, the inclusion of the concept of proximal salience helps to understand the etiology of the persistent and chronic psychoses and the role of the SN and in particular, the insula in the formation of the complex SCH symptoms, such as speech, thought and behavioral disorganization.

ARTICLE HIGHLIGHTS

Research background

The present resting-state functional magnetic resonance imaging (rs-fMRI) study was conducted in two groups of patients – schizophrenia (SCH) and individuals with mood disorders with the depressive syndrome (Ds) – to delineate the effective connectivity patterns at rest with the prior hypothesis that the salience network (SN) in SCH must have a fundamentally impaired connectivity, which prevents the switching between anticorrelated default mode network (DMN) and central executive network (CEN), thereby interfering with their basic functions and that this disruption may serve as neuroimaging biomarker to distinguish between the two groups of patients.

Research motivation

Our motivation to conduct such a comparative study comes from the lack of biological validity of available diagnostic tools, which ultimately leads to inaccurate diagnosis or high rates of comorbidity, and therefore an inadequate choice of treatment for psychotic and affective disorders.

Research objectives

By proving neurobiological markers to distinguish between SCH and mood disorders, we aimed to expand knowledge about their etiology and incorporate it into clinical practice, ultimately optimizing diagnosis and prognosis, and thus choosing the right treatment for these severe mental illnesses.

Research methods

The methods used include rs-fMRI and subsequent dynamic causal modeling (spDCM) to determine the direction and strength of connections to and from various nodes in the DMN, SN and CEN. The positive and negative syndrome scale was chosen for the assessment of the SCH group, and the severity of the Ds was assessed using the Montgomery–Åsberg Depression Rating Scale. The SPM 12 software running on MATLAB R2020b for Windows was used to perform data analysis. First level resting-state analysis was conducted using a general linear model. Regions of interest were predefined based on their involvement in the SN and the DNM. Furthermore, using the parametric empirical bayes method introduced in SPM12, the individual spDCM models were jointly estimated. Finally, the estimated spDCM models were used to extract connectivity strengths (A-matrix) for further statistical analysis in SPSS.

Research results

The coupling strengths of the connection from the precuneus (Pc) to the prefrontal cortex and from the anterior insula (aI) to the Pc, both inhibitory connections were present in the Ds group but absent in the SCH group. In the SCH patients, a significant excitatory connection from the dorsal part of the anterior cingulate cortex to the aI was present which was absent in the Ds study group.

Research conclusions

We managed to deliver evidence that despite the clinical overlaps, there are objective neuroimaging signatures of disease that can fundamentally distinguish SCH from mood disorders. The resting state of aberrant salience and proximal salience observed in the schizophrenic group has the potential to explain not only the psychotic symptoms, such as hallucinations and delusions, but also gives insight into the formation of the unique for SCH behavioral and thought disorganization.

Research perspectives

We suggest that our findings could help both in the biological understanding of the etiology of SCH and mood disorders in the development and improvement of the therapeutic approach. We visualize a future where translational neuroscience would ultimately integrate psychopathology, psychopharmacology, instrumental methods, and even neurosurgical techniques to restore brain imbalances by modulating the altered connectivity in the brains of people suffering from SCH and mood disorders.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1288-1300

DOI: 10.5498/wjp.v11.i12.1288

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Basic Study

Validity and reliability of the Dutch version of the displaced aggression questionnaire

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Author contributions: Smeijers D and Brazil IA translated the original DAQ to Dutch; The back-translation was evaluated by Denson TF; Smeijers D wrote the first draft of the manuscript; Brazil IA and Denson TF contributed significantly to the next versions of the manuscript; Bulten EH reviewed the manuscript; all authors approved its publication.

Institutional review board statement: The current study was approved by the institutional review board, No. ECSW2017-2306-520.

Conflict-of-interest statement: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data sharing statement: The statistical code and dataset are available from the corresponding author. Consent was not obtained for data sharing but the presented data are anonymized.

Country/Territory of origin: Netherlands

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Abstract

BACKGROUND

Displaced aggression occurs when a person encounters a provoking situation, is unable or unwilling to retaliate against the original provocateur, and subsequently aggresses against a target that is not the source of the initial provocation. The displaced aggression questionnaire (DAQ) was developed to measure individual differences in the tendency to displace aggression.

AIM

To develop a Dutch version of the DAQ and examine relationships between the DAQ and novel individual differences.

METHODS

The Dutch version of the DAQ was created using a back-translation procedure. Undergraduate students (n = 413) participated in the current study. The questionnaires were administered online.

RESULTS

The results confirmed the original three-factor structure and showed good reliability and validity. We also found differential relationships between trait displaced aggression, social anxiety and cognitive distortions.

CONCLUSION

Specialty type: Psychology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: April 26, 2021
Peer-review started: April 26, 2021
First decision: June 17, 2021
Revised: June 29, 2021
Accepted: November 5, 2021
Article in press: November 5, 2021
Published online: December 19, 2021

P-Reviewer: Ünver B
S-Editor: Wu YXJ
L-Editor: Webster JR
P-Editor: Wu YXJ

The results may indicate that distinct patterns exist in the development of the different dimensions of trait displaced aggression. This study adds to the growing cross-cultural literature showing the robustness of trait displaced aggression in several different cultures.

Key Words: Displaced aggression questionnaire; Displaced aggression; Questionnaire; Dutch translation; Psychometric properties

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Core Tip: The current study confirmed the original three-factor structure of the Displaced Aggression Questionnaire in a Dutch sample. We also found differential relationships between trait displaced aggression, social anxiety and cognitive distortions. The results may indicate that distinct patterns exist in the development of the different dimensions of trait displaced aggression. This study adds to the growing cross-cultural literature showing the robustness of trait displaced aggression in several different cultures.

Citation: Smeijers D, Denson TF, Bulten EH, Brazil IA. Validity and reliability of the Dutch version of the displaced aggression questionnaire. *World J Psychiatr* 2021; 11(12): 1288-1300
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1288.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1288

INTRODUCTION

Everyone experiences aggressive urges once in a while, but people are generally not very likely to "take these feelings out" on innocent others. Aggression is usually directed towards the source of provocation[1]. However, some factors can force us to displace our aggressive urges onto underserving others: When the source of frustration or the provocateur are not present and/or when someone is unable, unwilling or afraid to retaliate against the original provocateur[1-4]. Under any of these circumstances, aggression is redirected toward/displaced onto less powerful, easily available or seemingly innocent targets. The tendency to displace aggression is considered to be a stable trait that differs between individuals[5]. People with high inclinations towards displacing aggression seem more likely to aggress against undeserving others, such as coworkers, family members, or fellow drivers[5,6]. Also, individuals with the antisocial, borderline, and narcissistic personality disorder are thought to be more likely to exhibit trait displaced aggression, which highlights the clinical relevance of this phenomenon[7].

Trait displaced aggression consists of three dimensions: angry rumination (affective dimension), revenge planning (cognitive dimension) and behavioral displaced aggression (behavioral dimension)[5]. Angry rumination refers to perseverative thinking about a personally meaningful anger-inducing event[8]. Revenge planning is defined as engaging in thoughts about retaliation for a prior provocation[9]. Displaced aggression as a behavioral dimension is conceptualized as the tendency to act aggressively towards people other than the original source of a provocation[5]. It is thought that individuals high in trait displaced aggression use anger rumination to cope with life's provocations. Furthermore, individuals who take it out on others may be more likely to ruminate about the initial provocation[7], and are more likely to focus on their angry mood and to plan retaliation. Therefore, it is thought that ruminative activity maintains aggression-related affect, cognition, and arousal, through which negative emotional reactions toward those they subsequently encounter increase[5].

To assess individual differences in trait displaced aggression, Denson *et al*[5] developed the Displaced Aggression Questionnaire (DAQ). The DAQ consists of 31-items sub-divided in three subscales: angry rumination (*e.g.*, "I often find myself thinking over and over about things that have made me angry"), revenge planning (*e.g.*, "if somebody harms me, I am not at peace until I can retaliate") and behavioral displaced aggression (*e.g.*, "when angry, I have taken it out on people close to me").

All items are rated on a 7-point scale (1 = extremely uncharacteristic of me, 7 = extremely characteristic of me). The DAQ has high levels of internal consistency (Angry rumination α = 0.92; Revenge planning α = 0.91; Behavioral displaced aggression α = 0.91; total scale α = 0.95), exhibits good test-retest reliability at an interval of 4-wk (ranging from 0.75-0.80) and 11-wk (ranging from 0.78-0.89), and has good discriminant (*e.g.*, impulsivity, extroversion) and convergent validity (*e.g.*, physical and verbal aggression, anger coping styles). Finally, the DAQ predicted displaced aggression in a laboratory paradigm, domestic abuse, and road rage[5].

The DAQ has previously been translated into Romanian and Spanish. Both these adaptations confirmed the three-factor structure of the original questionnaire and showed good psychometric properties[10,11]. Both translations also confirmed positive associations with criterion measures (*e.g.*, trait anger, trait aggression, impulsivity, and big five personality traits), but did not explore any associations with other clinically relevant characteristics. For instance, Denson *et al*[5] suggested a potential association with fear or anxiety as their results showed an association between trait displaced aggression and behavioral inhibition. The authors reasoned that individuals high in trait displaced aggression are more likely to initially inhibit retaliatory responses when confronted with provocations. Subsequently, they withdraw from the provocation and continue to experience anger and conspire revenge. This association with behavioral inhibition and social withdrawal might also indicate that individuals high in trait displaced aggression experience elevated levels of withdrawal-related affect, such as anxiety and fear. Moreover, self-focused rumination is not only thought to generate and maintain anger, but also social anxiety (for review see[8,12]). It has also been suggested that anger rumination is associated with blame externalization and self-centeredness[8], also referred to as cognitive distortions. Cognitive distortions are defined as inaccurate thoughts, attitudes, or beliefs regarding own or others' behavior[13]. Previous studies have shown a strong association between such cognitive distortions and aggressive behavior[14-17]. However, the association with rumination and displaced aggression remains understudied. Elucidating the association between trait displaced aggression, social anxiety, and cognitive distortions will further increase our understanding of the mechanism of trait displaced aggression.

The current study sought to create and examine the validity and reliability of a Dutch version of the DAQ. The original three-factor structure was verified, and the convergent and discriminant validity were examined by investigating the association between the Dutch version of the DAQ and state and trait anger, physical aggression, verbal aggression, anger disposition, hostility, impulsivity and extraversion. Additionally, the association with social anxiety and cognitive distortions was examined. It was hypothesized that impulsivity, hostility, anger, and aggression were positively associated with displaced aggression. A negative association with extraversion was expected. Finally, a positive association was hypothesized between anger rumination and social anxiety, and between anger rumination and cognitive distortions related to blame externalization and self-centeredness.

MATERIALS AND METHODS

Participants

413 undergraduate students (82.6% female; 17.4% male) from Radboud University, Nijmegen participated in the current study. The mean age of the participants was 20.04 years (SD = 3.18) and the majority were undergraduates enrolled in social sciences (n = 310; 75%).

Materials

DAQ: The DAQ[5] consists of 31-items which assess trait displaced aggression and consists of three facets: Angry rumination (*e.g.*, "I keep thinking about events that angered me for a long time"), revenge planning (*e.g.*, "When someone makes me angry, I can't stop thinking about how to get back at this person") and behavioral displaced aggression (*e.g.*, "I take my anger out on innocent others"). The Dutch version of the DAQ was created in the current study (see Supplementary material).

Aggression questionnaire: The aggression questionnaire (AQ)[18] is a self-report questionnaire to assess an overall trait of aggression. It consists of 29 items which are divided into four subscales: physical aggression, verbal aggression, anger and hostility. The items are scored on a 5-point Likert scale (1 = extremely unlike me to 5 =

extremely like me). The Dutch translation has acceptable/good psychometric properties (Cronbach's α ranging from 0.51 to 0.86)[19]. In the present study, the internal consistency was acceptable to good (Cronbach's α ranging from 0.69 to 0.81).

How I think questionnaire: The How I think questionnaire (HIT)[13] is a 54-item self-report questionnaire to assess self-serving cognitive distortions. The items are divided into four cognitive distortion subscales (self-centered, blaming others, minimizing/labeling, assuming the worst) and four behavioral referent categories (physical aggression, opposition-defiance, lying, stealing). The cognitive distortion subscales refer to the actual distortions, whereas the behavioral referent categories concern the types of cognitive distortions that are related to antisocial behavior. Items have to be answered on a 6-point Likert scale (1 = totally agree to 6 = totally disagree). The Dutch translation has good reliability (Cronbach's α ranging from 0.90 to 0.94) and validity (all *R's* > 0.20)[20]. In the current study the internal consistency varied from acceptable to good (Cronbach's α ranging from 0.75 to 0.87).

State-Trait Anger Scale: The State-Trait Anger Scale (STAS)[21] has been designed to measure state and trait anger. It is a self-report questionnaire of 20 items subdivided into two subscales that capture state (10 items) and trait anger (10 items), respectively. State anger refers to an emotional condition of a patient, which is consciously experienced and fluctuates over time. Trait anger refers to the disposition to become angry, and is thought to be a stable personality quality and to differ greatly across individuals[22]. The Dutch translation has good reliability for trait anger (Cronbach's α = 0.78)[23]. The internal consistency was excellent in the current study (Cronbach's α for state anger = 0.91, trait anger = 0.87).

Novaco Anger Scale-Provocation Inventory: The Novaco Anger Scale-Provocation Inventory (NAS-PI)[24,25] consists of two parts: the NAS and the PI. The NAS assesses anger. It consists of 48 items that quantify things that people sometimes think, feel, and do. The items are subdivided in three subscales: Cognition, arousal and behavior, which are rated on a 3-point scale (1 = never true, 2 = sometimes true, 3 = always true). The PI consists of 25 items that refer to anger-eliciting situations that need to be rated on a 4-point scale (1 = not at all angry, 4 = very angry). The Dutch translation has excellent psychometric properties (Cronbach's α ranging from 0.92 to 0.95)[24]. The internal consistency was good in the current study (Cronbach's α ranging from 0.75 to 0.89).

Barratt Impulsivity Scale: The Barratt Impulsivity Scale (BIS-11)[26] is a 30-item self-report questionnaire that assesses individual differences in impulsivity. The BIS-11 measures 3 types of impulsivity defined as attentional impulsiveness, motor impulsiveness and non-planning impulsiveness. Items are rated on a 4-point scale ranging from 1 (rarely/never) to 4 (almost always/always). The Dutch translation has good psychometric properties (Cronbach's α = 0.81)[27]. Because we employed the BIS-11 as a measure for overall impulsivity, only the total score was used. In the current study the internal consistency was good (Cronbach's α = 0.81).

Ten-Item Personality Inventory: The Ten-Item Personality Inventory (TIPI)[28] is a 10-item self-report questionnaire to assess Big-Five personality dimensions. The TIPI consists of five subscales: extraversion, openness to experiences, emotional stability, conscientiousness and agreeableness. Items are rated on a 7-point scale (1 = strongly disagree, 7 = strongly agree). The Dutch translation has good convergent and discriminant validity (all *R's* > 0.20)[29]. In the current study, only the subscale extraversion showed good internal consistency (Cronbach's α = 0.72) and was, therefore, the only subscale of the TIPI used for the validation. For the other subscales Cronbach's α ranged from 0.28 to 0.59, indicating that these scales did not measure the target construct reliably.

Liebowitz Social Anxiety Scale: The Liebowitz Social Anxiety Scale (LSAS)[30,31] is a 24-item self-report questionnaire to assess social anxiety and avoidance. Each item is rated for level of fear (ranging from 0 = none to 3 = severe) and avoidance (ranging from 0 = none to 3 = almost always) it triggered in the past week. Both the original and the Dutch version have stable psychometric properties. In the current study the internal consistency was excellent (Cronbach's α = anxiety: 0.93, avoidance: 0.89).

Procedure

The Dutch version of the DAQ was created using a back-translation procedure. First, the original DAQ was translated to Dutch by Smeijers D and Brazil IA. Then, the first

Dutch version was translated back to English by a native English speaker. Finally, the back-translation was evaluated by Denson TF, who developed the original DAQ[5]. No content edits were made to the DAQ during the translation process.

The current study had a cross-sectional design. The questionnaires were administered online and were completed individually, with all the required information and instructions provided in writing. After receiving information about the nature of the study, participants signed a consent form. In total, it took participants approximately 60 min to complete the questionnaires. All participants received course credits for their participation. The current study was approved by the institutional review board (ECSW2017-2306-520).

Statistical analyses

First, the means, standard deviations, mean inter-item correlations, skewness and kurtosis statistics for the DAQ total and the individual subscale scores were calculated. Next, the internal reliability of the DAQ Dutch version in the current sample was investigated using Cronbach's α. Subsequently, a confirmatory factor analysis (CFA) was used to verify the three-factor model of the DAQ[5] and to test whether the three factors loaded on a general latent variable represented trait displaced aggression. The analysis was conducted with a WLSMV estimator in Mplus version 7[32]. The DAQ items are rated on a 7-point Likert scale, and thus yields ordinal data. Therefore, the WLSMV estimator was favored because it is specifically designed for categorical (*e.g.*, binary or ordinal) observed data (*e.g.*,[33]). Each item was constrained to load on one factor (*i.e.*, the original factor identified by Denson *et al*[5], 2006). Model fit was evaluated using absolute and conventional fit indices; the Chi-square statistic, the Tucker-Lewis index (TLI), and the comparative fit index (CFI), the root mean square error of approximation (RMSEA) model fit was considered to be good for CFI and TLI values greater than 0.90 and a non-significant Chi-square test ($P > 0.05$)[34-36]. For RSMEA, a value less than 0.06 was considered to be good, and a value between 0.05 and 0.10 was considered an acceptable fit[37]. A factor loading ≥ 0.4 was considered strong[38].

The convergent and discriminant validity were examined using correlation analyses. A bootstrapping procedure (5000 iterations) was used to determine 95%CI and to test the significance of the correlations. By bootstrapping, one is able to simulate the population distribution of the correlation and to provide confidence intervals for the correlation coefficients[39]. This approach yields more accurate estimates compared to estimates obtained without resampling, as would be the case in traditional parametric correlation analysis[40].

Finally, the relationships between the DAQ and social anxiety and cognitive distortions were explored in more detail. Specifically, unique patterns of social anxiety and cognitive distortions on anger rumination, revenge planning, and behavioral displaced aggression were examined. Bayesian path analyses were conducted using Mplus version 7[32]. Social anxiety and avoidance, and the cognitive distortions related to self-centeredness, blaming others, minimizing/mislabeling, and assuming the worst served as independent variables, while anger rumination, revenge planning, and behavioral displaced aggression served as dependent variables. Instead of the DAQ items, the DAQ subscales were now used. The subscales consisted of the mean of the corresponding items and were, therefore, on a continuous instead of an ordinal scale. In order to be able to compare the estimates, these variables were standardized by computing z-scores. All variables were treated as continuous, observed, variables. Path analysis was conducted with a Bayesian estimator (using the default Gibbs sampler PX1), 4 Markov Chain Monte Carlo chains and 100.000 iterations (of which the first 50.000 were used as burn-in trials) (see [16]). This analysis was exploratory in nature. Therefore, a Bayesian estimator was favored because it is data driven and, furthermore, avoids statistical assumptions about the distribution of the test statistics (*e.g.*,[41]).

In this study, a model was considered to show good fit if convergence was achieved with a proportional scale reduction ≤ 1.05[42]. Furthermore, the posterior predictive *P* value, a measure of similarity between observed and simulated data generated by the model being examined, should ideally be close to 0.5, which means that the model's predictions are consistent with the observed data[43]. Finally, the Chi-Square test to conduct Posterior Predictive Checking (with a 95% credibility interval; 95%CI) should include the value 0[42]. Significance of the regression weights were determined based on the 95%CIs of the Bayesian posterior distribution. The 95%CIs of the regression weights that did not contain the value 0 were considered significant.

RESULTS

Descriptive statistics and internal consistency

Descriptive statistics are displayed in Table 1. The internal consistency and mean inter-item correlations were found to vary from good to excellent for all subscales and the scale as a whole. Finally, all subscale scores correlated positively with each other (see Table 2).

Factor analysis

A CFA was conducted to verify the original three-factor solution of the DAQ. The CFA showed an acceptable fit: χ^2 (431) = 2034.65, $P < 0.001$; CFI = 0.92; TLI = 0.91; and RMSEA = 0.09. The items demonstrated good factor loadings (see Supplementary material). Additionally, the three factors loaded significantly (all *P's* < 0.001) on the superordinate latent variable for trait displaced aggression, and demonstrated high factor loadings (anger rumination = 0.792; revenge planning = 0.810; behavioral displaced aggression = 0.734), see Figure 1.

Construct validity

Anger rumination, revenge planning and behavioral displaced aggression were significantly positively correlated with the STAS state and trait anger, LSAS anxiety and avoidance, BIS-11, and all subscales of the AQ, HIT and the NAS and negatively with the TIPI extraversion subscale (see Table 2).

Path analysis

Social anxiety and avoidance, the four types of cognitive distortions, and anger rumination, revenge planning, and behavioral displaced aggression were included in the model. The path model is displayed in Figure 2, only significant results are displayed. The results revealed that social anxiety had a direct positive effect on anger rumination and behavioral displaced aggression (see Table 3). Cognitive distortions related to Blaming Others had a direct positive effect on behavioral displaced aggression, whereas cognitive distortions related to minimizing/mislabeling had a direct effect on revenge planning. The 95% credibility interval for the difference between the observed and the replicated Chi-square values is -20.76 to 21.43. Posterior predictive *P* value = 0.49, indicating an excellent model fit.

DISCUSSION

The current study examined the validity and reliability of the Dutch version of the DAQ. The results showed that the descriptive characteristics for the subscales of the Dutch DAQ were consistent with previous findings[5,11]. Furthermore, all subscales exhibited excellent reliability, and the inter-item correlations were good. Also, the original three-factor structure was confirmed in the current sample. However, the Chi-square value did not indicate a good fit, but this finding is in line with previous research[10,11]. It is important to note that this statistic is sensitive to sample size and often rejects the model when large samples are used[34]. In combination with the good values for CFI and TLI, the acceptable value for RMSEA, and the good factor loadings, the model showed acceptable fit. Finally, the three factors loaded significantly on a general latent variable. This finding provides support for the notion that anger rumination, revenge planning, and behavioral displaced aggression reflect dimensions of the general construct of trait displaced aggression. The current findings indicate that the proposed three-factor structure for the DAQ scales extends to the Dutch version and showed the robustness of trait displaced aggression cross-culturally.

Furthermore, all subscales correlated in the expected directions with the criterion measures; positive associations were found with hostility, impulsivity, and several forms of anger and aggression and a negative association was found with extraversion, which is in line with previous studies[5,10,11]. Additionally, a positive association was found with two other clinically relevant characteristics; social anxiety and several forms of cognitive distortions. Specifically, it was found that a high score on all three dimensions of trait displaced aggression were associated with high social anxiety and the tendency to avoid social situations. Denson *et al*[5] suggested a possible relation between trait displaced aggression and fear and anxiety. The current findings provide support for this notion. Based on the confidence intervals and effect sizes, it seemed that the association was the strongest with anger rumination. This may suggest that anxious individuals are more internally focused, which is also supported

Table 1 Descriptive characteristics of the Dutch displaced aggression questionnaire

	α	*r*	mean ± SD	Skewness	SE	Kurtosis	SE
Anger rumination	0.924	0.552	3.36 ± 1.32	0.474	0.12	-0.437	0.24
Behavioral displaced aggression	0.925	0.558	2.43 ± 1.13	0.909	0.12	0.545	0.24
Revenge planning	0.921	0.556	1.89 ± 0.97	2.138	0.12	5.376	0.24
Total	0.95	0.392	2.56 ± 0.94	0.992	0.12	1.498	0.24

r: Inter-item correlations; SD: Standard deviation; SE: Standard error.

by the aforementioned negative association with extraversion.

Additionally, the results of the path analysis showed that social anxiety indeed had the strongest relation with anger rumination but also with behavioral displaced aggression. It can be speculated that anxious individuals may act out their anger less easily and withdraw from provoking situations. Consequently, they seem to be more likely to ruminate about anger-provoking events, which in turn could increase the risk of behavioral displaced aggression[5]. Social anxiety is characterized by the fear that your behavior/performance will be evaluated as humiliating or embarrassing[44]. This fear may inhibit any form of acting out towards the original (less familiar) provocateur. However, among close others, social anxious individuals may not experience this intense fear[45], because they probably have learned that close others will support them regardless of their performance. This may induce a sense of safety. When feeling safe, it might be easier to vent (suppressed) feelings. Individuals high in trait anger and aggression and with high levels of social anxiety may avoid acting out their anger in provoking situations, but displace aggression towards close others. This combination of characteristics might play a role in the mechanism behind, for instance, domestic violence.

Also, the correlations with cognitive distortions may provide some additional evidence for an internal focus in individuals high in trait displaced aggression. Specifically, when comparing the confidence intervals and effect sizes, it seemed that all cognitive distortions showed a stronger association with revenge planning, which was contrary to our hypothesis. The findings of the path analysis showed that cognitive distortions related to minimizing/mislabeling had the strongest relation with revenge planning. Cognitive distortions of this type refer to depicting antisocial behavior as being acceptable, causing no real harm, or referring to others with a dehumanizing label[13]. It may be that such cognitive distortions have a reinforcing effect on revenge planning by easily justifying antisocial behavior in general and possibly retaliation in specific.

Additionally, cognitive distortions related to Blaming Others were most strongly related to behavioral displaced aggression. Distortions of this type refer to the misattribution of blame to outside sources or misattributing misfortune to innocent others [13]. Such distortions might increase the risk of displaced aggression as believing that others are the ones to blame probably easily justifies acting out anger or aggression. Contrary to our hypothesis, the path analysis did not indicate an association between trait displaced aggression and cognitive distortions related to self-centeredness. Cognitive distortions of this type refer to acquiring status to one's own needs, views, expectations, and desires to such a degree that the legitimate views of others are scarcely considered or even disregarded[13]. These types of distortions might play a role in the emergence of an aggressive conflict. However, it also may be suggested that due to such distortions the focus is too much on the self that it might even limit or distract from any angry feelings causing no rumination or displaced aggression. Also, a different view of another might not even induce anger as someone else's opinion will be disregarded.

Generally, cognitive distortions are thought to be strongly related to externalizing behaviors (for a meta-analysis see[46]). Cognitive distortions might play a role in neutralizing feelings of blame and preserving a positive self-image. If the individual has learned that this can be achieved through inappropriate use of aggression and/or antisocial behavior, cognitive distortions may strengthen or maintain such maladaptive tendencies to protect the self-image[14,47]. Also, the more persistent such distortions are, the more difficult adjusting maladaptive tendencies will be (see[48]). The current findings are also in line with other studies showing different patterns of associations between distinct types of cognitive distortions and subtypes of aggression.

Table 2 Correlations between the displaced aggression questionnaire and the State-Trait Anger Scale, Liebowitz Social Anxiety Scale, Barratt Impulsivity Scale, Ten-Item Personality Inventory extraversion, Aggression questionnaire, How I think questionnaire, and the Novaco Anger Scale

	Anger rumination	Behavioral displaced aggression	Revenge planning
Anger rumination	-	r = 0.529[c], 95%CI = 0.452-0.599	r = 570[c], 95%CI = 0.499-0.631
Behavioral displaced aggression	r = 0.529[c], 95%CI = 0.452-0.599	-	r = 0.510[c], 95%CI = 0.406-0.602
Revenge planning	r = 0.570[c], 95%CI = 0.499-0.631	r = 0.510[c], 95%CI = 0.406-0.602	-
STAS state	r = 0.317[c], 95%CI = 0.233-0.398	r = 0.290[c], 95%CI = 0.204-0.385	r = 0.465[b], 95%CI = 0.323-0.597
STAS trait	r = 0.475[c], 95%CI = 0.389-0.556	r = 0.515[c], 95%CI = 0.415-0.605	r = 0.546[b], 95%CI = 0.420-0.665
LSAS anxiety	r = 0.320[c], 95%CI = 0.230-0.408	r = 0.267[c], 95%CI = 0.159-0.371	r = 0.253[b], 95%CI = 0.123-0.381
LSAS avoidance	r = 0.308[c], 95%CI = 0.214-0.404	r = 0.236[c], 95%CI = 0.133-0.337	r = 0.263[b], 95%CI = 0.156-0.376
BIS-11 total	r = 0.185[c], 95%CI = 0.088-0.274	r = 0.200[c], 95%CI = 0.105-0.288	r = 0.379[c], 95%CI = 0.283-0.469
TIPI extraversion	r = -0.099[a], 95%CI = -0.181-0.000	r = -0.034, 95%CI = -0.127-0.064	r = -0.111[a], 95%CI = -0.198--0.014
AQ physical	r = 0.311[c], 95%CI = 0.215-0.399	r = 0.332[c], 95%CI = 0.232-0.425	r = 0.611[b], 95%CI = 0.516-0.698
AQ verbal	r = 0.250[c], 95%CI = 0.161-0.346	r = 0.259[c], 95%CI = 0.173-0.351	r = 0.321[b], 95%CI = 0.236-0.409
AQ anger	r = 0.511[c], 95%CI = 0.429-0.587	r = 0.581[c], 95%CI = 0.491-0.664	r = 0.497[b], 95%CI = 0.382-0.597
AQ hostility	r = 0.502[c], 95%CI = 0.419-0.581	r = 0.411[c], 95%CI = 0.320-0.501	r = 0.481[b], 95%CI = 0.381-0.571
HIT self-centered	r = 0.215[c], 95%CI = 0.123-0.307	r = 0.325[c], 95%CI = 0.225-0.416	r = 0.517[b], 95%CI = 0.412-0.612
HIT blaming others	r = 0.275[c], 95%CI = 0.193-0.349	r = 0.370[c], 95%CI = 0.283-0.452	r = 0.557[b], 95%CI = 0.459-0.652
HIT minimizing/mislabeling	r = 0.267[c], 95%CI = 0.178-0.349	r = 0.321[c], 95%CI = 0.220-0.411	r = 0.588[b], 95%CI = 0.494-0.674
HIT assuming the worst	r = 0.278[c], 95%CI = 0.201-0.351	r = 0.329[c], 95%CI = 0.232-0.422	r = 0.542[b], 95%CI = 0.428-0.643
HIT opposition defiance	r = 0.312[c], 95%CI = 0.222-0.397	r = 0.387[c], 95%CI = 0.295-0.473	r = 0.586[b], 95%CI = 0.488-0.676
HIT physical aggression	r = 0.286[c], 95%CI = 0.200-0.364	r = 0.360[c], 95%CI = 0.272-0.445	r = 0.617[b], 95%CI = 0.518-0.705
HIT lying	r = 0.278[c], 95%CI = 0.186-0.368	r = 0.298[c], 95%CI = 0.218-0.388	r = 0.461[c], 95%CI = 0.369-0.554
HIT stealing	r = 0.122[a], 95%CI = 0.042-0.204	r = 0.239[c], 95%CI = 0.144-0.336	r = 0.432[c], 95%CI = 0.309-0.543
NAS cognition	r = 0.572[c], 95%CI = 0.487-0.649	r = 0.441[c], 95%CI = 0.336-0.530	r = 0.539[c], 95%CI = 0.420-0.635
NAS arousal	r = 0.638[c], 95%CI = 0.566-0.704	r = 0.542[c], 95%CI = 0.442-0.622	r = 0.534[c], 95%CI = 0.420-0.636
NAS behavior	r = 0.417[c], 95%CI = 0.329-0.501	r = 0.504[c], 95%CI = 0.411-0.588	r = 0.640[c], 95%CI = 0.528-0.734
NAS PI	r = 0.417[c], 95%CI = 0.325-0.505	r = 0.434[c], 95%CI = 0.347-0.516	r = 0.412[c], 95%CI = 0.329-0.503

[a]P < 0.05.
[b]P < 0.02.
[c]P < 0.001. CI: Confidence interval; STAS: State-Trait Anger Scale; LSAS: Liebowitz Social Anxiety Scale; BIS-11: Barratt Impulsivity Scale; TIPI: Ten-Item Personality Inventory; AQ: Aggression questionnaire; HIT: How I think questionnaire; NAS: Novaco Anger Scale; PI: Provocation Inventory.

For instance, it has been found that cognitive distortions related to physical aggression were associated with the actual disposition to use physical aggression. Another example is that verbal aggressive behavior was most strongly associated with cognitive distortions related to opposition-defiance (*i.e.*, disrespecting rules, laws, and authority and external reasons for deviant behavior)[14,16]. Another novel finding was that social anxiety and cognitive distortions were differentially related to the subscales of the DAQ. This might suggest that distinct patterns exist in the development of the different dimensions of trait displaced aggression. However, it is important to note that some of the estimated effect sizes in the path analysis were rather low (*e.g.*, β 0.171 and β 0.184). Also, the cross-sectional design of the current study does not allow for strong claims concerning causality. Thus, the results have to be interpreted with caution. Prospective research is needed to elucidate the role of social anxiety and cognitive distortions in further detail, but also to elucidate potential distinct patterns in the development of trait displaced aggression.

Table 3 Standardized results of Bayesian path analysis with 95% credibility intervals

Dependent variable	Parameter	Estimate (β)	95%CI (lower 2.5%-upper 2.5%)
Anger rumination	Social anxiety	**0.171**	(0.003, 0.335[1])
	Social avoidance	0.095	(-0.072, 0.26)
	Cognitive distortions SC	-0.069	(-0.237-0.102)
	Cognitive distortions BO	0.05	(-0.155, 0.253)
	Cognitive distortions MM	0.091	(-0.103, 0.283)
	Cognitive distortions AW	0.132	(-0.075, 0.335)
Revenge planning	Social anxiety	0.042	(-0.103, 0.185)
	Social avoidance	0.048	(-0.097, 0.192)
	Cognitive distortions SC	0.037	(-0.11, 0.183)
	Cognitive distortions BO	0.157	(-0.02, 0.331)
	Cognitive distortions MM	**0.357**	(0.189, 0.519[1])
	Cognitive distortions AW	0.042	(-0.137, 0.219)
Behavioral displaced aggression	Social anxiety	**0.184**	(0.017, 0.346[1])
	Social avoidance	-0.018	(-0.183, 0.148)
	Cognitive distortions SC	0.114	(-0.055, 0.281)
	Cognitive distortions BO	**0.259**	(0.057, 0.455[1])
	Cognitive distortions MM	-0.015	(-0.207, 0.176)
	Cognitive distortions AW	-0.03	(-0.232, 0.175)

[1]Statistically significant predictors are flagged. CI: Credibility intervals; SC: Self-centered; BO: Blaming others; MM: Minimizing/labeling; AW: Assuming the worst.

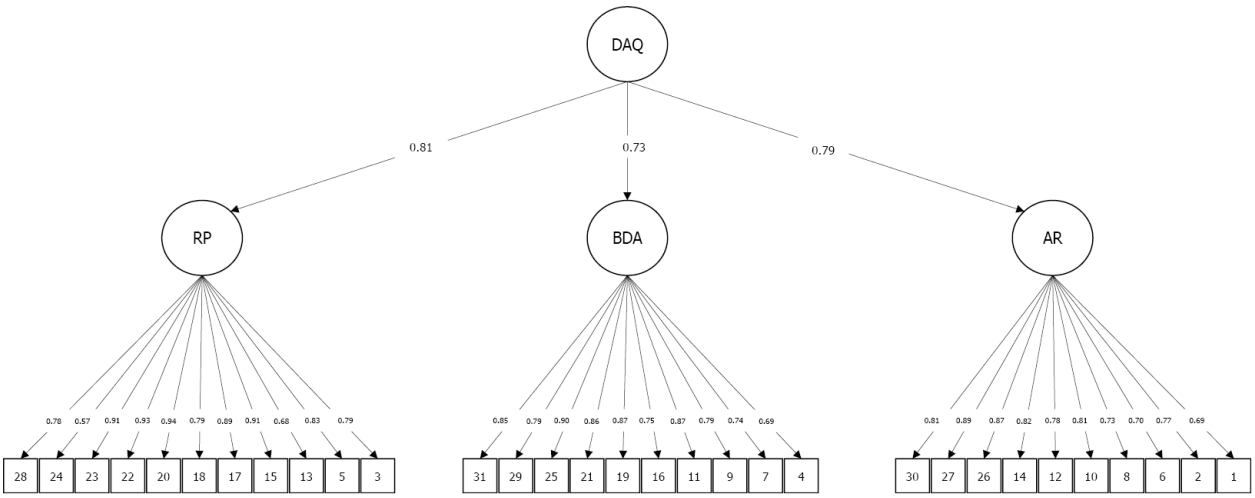


Figure 1 Factor structure of the Dutch displaced aggression questionnaire. Standardized factor loadings are displayed. DAQ: Displaced aggression questionnaire; RP: Revenge planning; BDA: Behavioral displaced aggression; AR: Anger rumination.

The present research allowed us to test aspects of the multiple system models of angry rumination[8]. According to the model, following a provocation, some people are more likely to ruminate than other people. Trait displaced aggression is one such individual difference that increases the likelihood of rumination following provocation. The influence of trait displaced aggression on actual aggressive behavior is subsequently moderated by the cognitive features of the rumination itself (called the "cognitive level" in the model). Because we know little of the cognitive content of the rumination associated with trait displaced aggression, in the present research, we

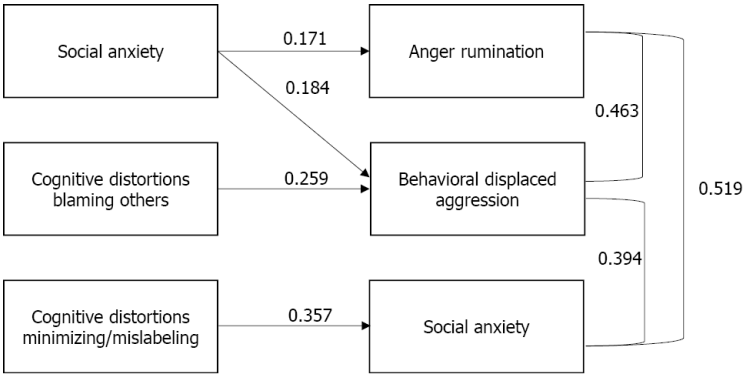


Figure 2 Standardized regression weights in the Bayesian path model. Only significant results are displayed in order to maintain readability.

assessed various aggression-related cognitive distortions. This allowed us to investigate the extent to which these cognitive distortions characterize individual differences in trait displaced aggression. Doing so may expand the multiple system models by providing novel information on the content of angry rumination among people high in trait displaced aggression.

Trait displaced aggression is thought to be an important contributor to the development of aggression. It is considered to be a personality characteristic, which means that through the repeated use of aggression individuals high in trait displaced aggression have developed aggressive schemas and knowledge structures[5]. Consequently, they have acquired strong associations between provocations and aggressive affect, arousal, and cognition. These internal processes are highly likely to contain anger rumination and revenge planning and presumably linger for a longer period of time[5]. This in turn increases the likelihood of engaging in aggressive acts. Therefore, trait displaced aggression is of great importance in understanding and explaining aggression, such as in the context of domestic violence and road-rage. More insight in distinct developmental patterns could determine which dimension of trait displaced aggression will be most prominent in a specific individual. In particular, this is important for clinical practice as this would foster the development of targeted interventions that fit the needs of individual patients.

One potential limitation of the present study is that the sample consisted primarily of female participants. The results might therefore not be generalizable to men. This gender disbalance is in line with previous studies[5,10]. Moreover, these studies found no or only small gender differences on DAQ scores. This may suggest that males and females are relatively similar in trait displaced aggression. Future research has to elucidate possible gender differences in further detail in samples consisting of an equal quantity of males/females. Second, the current sample consisted of undergraduate students not typified by clinical levels of aggression. Even though everyone experiences aggressive urges once in a while, the majority often does not have difficulties in controlling their aggressive impulses. Severe problems in regulating aggressive impulses might be strongly related to acting out on innocent others. Such behavior is often seen in cases of domestic violence, victims of bullying and traumatized individuals. Future research should include a sample of individuals displaying severe levels of aggression to elucidate the reliability and validity of the DAQ in aggressive samples. Including clinical samples could also reveal similarities and/or differences between the mechanism behind displaced aggression in different contexts. Third, criterion validity and test-retest reliability were not examined in the current study. Future research should elucidate whether the Dutch version of the DAQ can also be used for repeated measurements.

CONCLUSION

Notwithstanding the limitations, the results encourage the use of the Dutch version of the DAQ to measure individual differences in trait displaced aggression. This study adds to the growing cross-cultural literature showing the robustness of trait displaced aggression in several different cultures. The measurement of individual differences in trait displaced aggression might be a starting point for reducing for instance domestic violence, workplace aggression, and road rage[5]. Once the current findings are

confirmed in aggressive samples, an important next step would be to investigate whether currently used general aggression interventions (*e.g.*, Aggression Replacement Training)[49] also reduce anger rumination, revenge planning, and behavioral displaced aggression. If these interventions do not suffice, specific interventions need to be developed to treat the different dimensions of trait displaced aggression. The DAQ is likely to be a valuable instrument to assess trait displaced aggression in clinical settings.

ARTICLE HIGHLIGHTS

Research background

Displaced aggression occurs when a person encounters a provoking situation, is unable or unwilling to retaliate against the original provocateur, and subsequently aggresses against a target that is not the source of the initial provocation. Trait displaced aggression consists of three dimensions: Angry rumination, revenge planning, and behavioral displaced aggression. The displaced aggression questionnaire (DAQ) was developed to measure individual differences in the tendency to displace aggression. Previous studies, however, did not explore any associations with other clinically relevant characteristics.

Research motivation

Elucidating the association between trait displaced aggression, social anxiety, and cognitive distortions will further increase our understanding of the mechanism of trait displaced aggression.

Research objectives

The current study developed a Dutch version of the DAQ and examined relationships between the DAQ and novel individual differences.

Research methods

A sample of undergraduate students (n = 413) participated in the current study. The DAQ was translated using a back-translation procedure. Subsequently, the Dutch DAQ, aggression questionnaire, How I think questionnaire, State-Trait Anger Scale, Novaco Anger Scale-Provocation Inventory, Barratt Impulsivity Scale, Ten-Item Personality Inventory, and the Liebowitz Social Anxiety Scale were administered in an online survey.

Research results

The results confirmed the original three-factor structure and showed good reliability and validity. We also found differential relationships between trait displaced aggression, social anxiety and cognitive distortions.

Research conclusions

The results encourage the use of the Dutch version of the DAQ to measure individual differences in trait displaced aggression. The results might indicate that distinct patterns exist in the development of the different dimensions of trait displaced aggression. This study adds to the growing cross-cultural literature showing the robustness of trait displaced aggression in several different cultures.

Research perspectives

Once the current findings are confirmed in aggressive samples, an important next step would be to investigate whether currently used general aggression interventions also reduce anger rumination, revenge planning, and behavioral displaced aggression.

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World Journal of Psychiatry

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World J Psychiatr 2021 December 19; 11(12): 1301-1313

DOI: 10.5498/wjp.v11.i12.1301

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

BDNF methylation and mRNA expression in brain and blood of completed suicides in Slovenia

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Author contributions: Videtic Paska A and Ropret S designed the study and the experiments; Zupanc T collected patient data, brain tissue, and blood samples; Ropret S performed the majority of experiments, analyzed the data, and wrote the manuscript; Kouter K performed DNA extraction, bisulfite conversion of DNA, and helped with RNA extraction; Videtic Paska A corrected the manuscript; all the authors approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Medicinal Ethics Committee of the Republic of Slovenia, No. 47/12/12.

Informed consent statement: The samples included in the study are post mortem samples collected during the course of autopsy at the Institute of Forensic Medicine, University of Ljubljana. The collected samples were used for routine analyses associated with the autopsy as well as for the

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Abstract

BACKGROUND

Suicide is a major public health problem. Worldwide, around 800000 people die by suicide every year. Suicide is a multifactorial disorder, with numerous environmental and genetic risk factors involved. Among the candidate genes, changes in the *BDNF* locus at the gene, epigenetic, mRNA, and protein expression levels have been implicated in psychiatric disorders, including suicidal behavior and completed suicides.

AIM

To investigate changes in *BDNF* methylation and expression of four alternative *BDNF* transcripts for association with completed suicide.

METHODS

This case-control study included 42 unrelated male Caucasian subjects, where 20 were control subjects who died following acute cardiac arrest, and 22 were suicide victims who died by hanging. DNA and RNA were extracted from brain tissue (Brodmann area 9 and hippocampus) and from blood. DNA methylation and mRNA expression levels were determined by targeted bisulfite next-generation sequencing and reverse-transcription quantitative PCR. Statistical analysis was done by use of two-tailed Student's *t* tests for two independent samples, and the Benjamini-Hochberg procedure was implemented for correction for multiple comparisons.

RESULTS

In DNA from brain tissue, there were no significant differences in *BDNF* methylation between the study groups. However, data showed significantly reduced DNA methylation of the *BDNF* region upstream of exon I in blood

molecular-genetic analyses. In Slovenia use of post mortem samples does not include use of informed consent, but the collection and use of the samples has to be approved by the Medicinal Ethics Committee of the Republic of Slovenia. For the collected samples the approval of the Medicinal Ethics Committee is attached.

Conflict-of-interest statement: None to declare.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Supported by Slovenian Research Agency, No. P1-0390, and No. J3-7132.

Country/Territory of origin: Slovenia

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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samples of suicide victims compared to the controls (5.67 ± 0.57 *vs* 6.83 ± 0.64, P_{corr} = 0.01). In Brodmann area 9 of the brain of the suicide victims but not in their hippocampus, there was higher expression of *BDNF* transcript I-IX (NM_170731.4) compared to the controls (0.077 ± 0.024 *vs* 0.05 ± 0.013, P = 0.042). In blood, expression analysis for the *BDNF* transcripts was not feasible due to extensive RNA degradation.

CONCLUSION

Despite the limitations of the study, the obtained data further support a role for BDNF in suicidality. However, it should be noted that suicidal behavior is a multifactorial disorder with numerous environmental and genetic risk factors involved.

Key Words: Suicidal behavior; Epigenetics; Next-generation sequencing; Brain; Blood; Caucasian

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Core Tip: *BDNF* methylation analysis of brain tissues did not show differences between control subjects and suicide victims, although there was higher expression of *BDNF* transcript I-IX in Brodmann area 9 of the suicide victims. Furthermore, the data obtained from blood were interesting, especially in terms of the direction of the effects. Although due to the extensively degraded RNA in the blood, we were not able to confirm these effects on mRNA expression. Although suicide is a multifactorial disorder, our data overall further support the previously implicated role of BDNF in suicidality.

Citation: Ropret S, Kouter K, Zupanc T, Videtic Paska A. *BDNF* methylation and mRNA expression in brain and blood of completed suicides in Slovenia. *World J Psychiatr* 2021; 11(12): 1301-1313
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1301.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1301

INTRODUCTION

Suicide is a major public health problem. Globally, around 700000 people die by suicide every year. Indications are that for every completed suicide, there will have been more than 20 'unsuccessful' suicide attempts[1]. Suicide is the final and extreme act in the continuum of intentional self-destruction by a suicidal subject. Suicidal behaviors are complex and heterogeneous, and they result from interactions between numerous environmental and genetic risk factors[2,3]. Indeed, part of the genetic component of suicide risk is determined by epigenetic factors. These are heritable and can be modified under environmental influences, which can result in altered gene expression without any changes to the DNA nucleotide sequence[3-5].

A number of candidate genes have already been shown to have associations with psychiatric disorders, including suicide and other related behaviors. Among these is a member of the neurotrophin family encoding *BDNF*[6,7]. BDNF is a nerve growth factor that has an important role in the development of the central nervous system as well as in the regulation of structural, synaptic, and morphological plasticity in adults [8]. BDNF acts through its binding to two distinct receptors: Neurotrophic tyrosine receptor kinase 2 and nerve growth factor receptor (also known as p75 neurotrophin receptor)[9].

BDNF is a secreted protein that is synthesized as a pre-proBDNF precursor. After removal of the signal peptide, proBDNF is proteolytically cleaved into the pro-peptide and the mature BDNF. However, not only the mature BDNF but also proBDNF and the released BDNF pro-peptide are functionally active. A role for the pro-peptide itself has only recently been acknowledged[9,10].

The human *BDNF* locus spans approximately 70 kb of chromosome 11 and has a complex structure. It includes 11 exons (I-V, Vh, VI-VIII, VIIIh, IX), of which 9 have

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Received: March 16, 2021
Peer-review started: March 16, 2021
First decision: May 5, 2021
Revised: May 25, 2021
Accepted: September 16, 2021
Article in press: September 16, 2021
Published online: December 19, 2021

P-Reviewer: Oltra E, Soriano-Ursúa MA
S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Li JH

functional promotors and 4 contain alternative splice sites. The sequence that encodes the BDNF precursor form (*i.e.* pre-proBDNF) is located within exon IX[11], while the other exons are not translated. The complexity of the *BDNF* locus enables specific and precise temporal and tissue regulation of *BDNF* expression as well as regulation of its expression in response to the environment[11,12].

Given the roles of BDNF during development of the nervous system and regulation of brain plasticity in adults, it is not surprising that BDNF is emerging as one of the key factors in the development of mental disorders. Indeed, genetic[13] and epigenetic changes in the *BDNF* locus[14] and changes in *BDNF* mRNA and/or protein expression levels[14-18] have already been implicated in suicide.

Numerous studies[19-26] have defined links between epigenetic processes and mental disorders, including for nonfatal suicidal behavior, with DNA methylation established as the most studied mammalian epigenetic mechanism. These studies have shown that *BDNF* methylation in blood of subjects with mental disorders is usually higher than for that of control subjects. However, studies on *BDNF* methylation specifically in completed suicides are rare. Targeted and whole-genome methylation analyses were used in two studies that showed higher *BDNF* methylation in the brains of suicide victims compared to controls[14,27]. Interestingly, a recent study from our group where we also used a whole-genome methylation approach did not show the *BDNF* locus as differentially methylated in the brains of suicide victims when compared to controls[28].

In contrast to these few studies that have explored *BDNF* methylation in completed suicides, studies that have examined the expression of *BDNF* in suicide victims are more abundant. Some of these studies involved subjects who had been diagnosed with psychiatric disorders prior to dying by suicide. Nonetheless, the prevailing majority of these studies has shown that *BDNF* expression at the mRNA and/or protein levels is downregulated in several brain regions of suicide victims[14-18,29-31]. Keller *et al*[14] demonstrated a correlation between *BDNF* methylation and its expression at the mRNA level.

In terms of *BDNF* expression at the mRNA level, the vast majority of studies have examined total *BDNF* mRNA levels. Two studies, however, explored *BDNF* expression with regards to alternative mRNAs transcribed from the *BDNF* locus[30,31]. Wong *et al*[30] investigated the four most abundant and best characterized *BDNF* alternate transcripts (*i.e.* I-IX, II-IX, IV-IX, VI-IX) and showed significant upregulation of *BDNF* transcript I-IX (5'-exon = exon I) in patients with schizophrenia who died by suicide. They also reported similar trends for *BDNF* transcripts II-IX and IV-IX[30]. Reinhart *et al*[31] instead examined total *BDNF* mRNA levels and the levels of alternative mRNAs transcribed from the *BDNF* locus in several brain regions of patients with major depression disorder, bipolar disorder, and schizophrenia. Among all of these patients, about 37 % had died by suicide. The total *BDNF* mRNA levels did not differ from the controls across these brain regions and disease states. However, interestingly, they showed differences in expression of the alternative *BDNF* mRNAs[31,32].

To date, the studies that have explored methylation and/or expression of the *BDNF* locus for association with suicide at different levels have been performed with brain tissue only, with no similar approaches applied to blood. However, these data have shown that despite the multifactorial and polygenic nature of suicide and related behaviors, disturbances in the *BDNF* locus might make important contributions to the development of psychiatric disorders, including suicide and related behaviors. Therefore, further studies are needed to understand its role better.

Slovenia is a small European country that has a disproportionately high suicide rate. According to the latest suicide figures available from the World Health Organization in 2016, Slovenia ranked 13th highest globally and 9th highest in Europe. Despite the previous decline in the suicide rate in Slovenia from 2007, suicide still remains a serious public health problem. Combined with previous studies from our and other research groups, this encouraged us to investigate methylation of the *BDNF* gene and its expression levels in both brain tissue and blood from suicide victims and control subjects in the Slovenian population.

MATERIALS AND METHODS

Study subjects

This study included 42 unrelated male Caucasian subjects, where 20 were control subjects who died following acute cardiac arrest, and 22 were suicide victims who died by hanging. The patient data, brain tissue samples, and blood samples were collected

during regular autopsy procedures in 2014 and 2015 at the Institute of Forensic Medicine, Faculty of Medicine, University of Ljubljana (Ljubljana, Slovenia). The samples were stored at –80 °C prior to being processed.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (Approval N° 47/12/12).

Experimental procedures

***BDNF* methylation**: For the samples from both the control subjects and the suicide victims, the differences in methylation levels of five *BDNF* regions of interest (ROIs) in or near the CpG islands (regions with high frequency of CpG) were studied by next-generation sequencing (NGS) of bisulfite-converted DNA. The ROIs for methylation of *BDNF* were I1, I2, II, IV, and VI, as shown in Supplementary Figure 1, relative to the positions of the *BDNF* CpG islands and exons. The chromosomal coordinates and further details for the nucleotide sequences are given in Supplementary Figure 2.

Genomic DNA was extracted from 25 mg to 30 mg liquid nitrogen pulverized brain tissue from Brodmann area 9 (BA9) and hippocampus and from 200 µL blood from the right femoral vein. The DNA was extracted (QIAmp DNA mini kits; Qiagen, United States), according to the manufacturer's instructions, with the quantities and qualities of the DNA determined spectrophotometrically using a microplate reader (Synergy H4 Hybrid; BioTek, United States).

The DNA (1.0 µg) was subjected to sodium bisulfite conversion (EpiTect bisulfite kits; Qiagen, United States), according to the manufacturer's instructions. Then 20 ng to 40 ng of the bisulfite-converted DNA was used as templates for amplicon preparation for library construction. Amplicons were prepared by two rounds of PCR, according to the universal tailed experimental design and in such a way that sequencing was bidirectional (Guidelines for Amplicon Experimental Design, Roche, April 2014). In the first round of PCR, the *BDNF* ROIs were amplified with simultaneous addition of universal sequences. The specific parts of the fusion primers were designed using the Methyl Primer Express v1.0 software (Applied Biosystems, United States) and are listed in Supplementary Table 1. The universal sequences of the products from the first round of PCR were targeted in the second round of PCR by fusion primers that were labeled by the NGS system (454 Junior; Roche, Germany) adaptor and Multiplex Identifier sequences for sample identification. The reaction mixtures and cycling conditions for first and second rounds of PCR are given in Supplementary Tables 2 and 3, respectively. After each round, the samples were checked for the correct length of the amplicons on 2% agarose gels.

The amplicons from the second round of PCR were purified (Agencourt AMPure XP PCR purification system; Beckman Coulter, United States), with the purities determined on 2% agarose gels. The purified amplicons were precisely quantified using dsDNA assay kits (Quant-iT PicoGreen; Thermo Fisher Scientific, United States). The procedures for the purification and quantification of the amplicons was according to the Amplicon Library Preparation Manual (Roche, April 2014). Each amplicon solution was diluted to 10^9 amplicon molecules/µL. The amplicon library was prepared by pooling equal volumes of these diluted amplicon solutions. Then the library was diluted to the final concentration of 10^6 amplicon molecules/µL, with RNA/DNA quantification on a bioanalyzer (High Sensitivity DNA kits; Agilent Technologies, United States). The library was prepared and quantified according to Amplicon Library Preparation Manual (Roche, April 2014). The library was clonally amplified by emulsion PCR (emPCR Amplification Manual Lib-A; GS Junior and GS Junior+ Series; Roche, April 2014).

The libraries prepared from brain tissue (*i.e.* BA9, hippocampus) and from blood were sequenced in two separate runs on an NGS system (454 Junior; Roche, Germany), according to Sequencing Manual (GS Junior Titanium Series; Roche, January 2013).

***BDNF* mRNA expression:** The expression levels of *BDNF* transcripts NM_170731.4, NM_170732.4, NM_170733.3, and NM_170735 were determined by reverse transcription-quantitative PCR for the samples from the control subjects and the suicide victims.

Total RNA was extracted from 10 mg to 15 mg liquid nitrogen pulverized tissue from the BA9 and hippocampus brain regions and from 4 mL to 7 mL of blood from the right femoral vein using TRI Reagent solution (Sigma-Aldrich, Germany), according to the manufacturer instructions. RNA quantity and quality were determined spectrophotometrically (NanoDrop ND-1000; Thermo Scientific, United States) and by determination of the RNA Integrity Number on a bioanalyzer (Agilent) using kits (RNA 6000 nano kits; Agilent Technologies, United States).

Then, 3 μg total RNA (in 20 μL) from BA9, hippocampus, and blood of each subject were treated with DNase I and then reverse transcribed. The DNase I reaction mixture (total volume, 25 μL) also included 2.5 μL 10× buffer (Cat. #04 716 728 001; Roche, Germany), 0.2 μL DNase I (Cat. #04 716 728 001; Roche, Germany), and 2.3 μL double-distilled water. The treatment (thermocycler: GenAmp 2700; Applied Biosystems, United States) was for 10 min at 30 °C for DNA degradation, followed by 10 min at 75 °C for DNase I inactivation. The reverse transcription (Transcriptor Universal cDNA Master; Roche, Germany) reaction mixture (final volume, 40 μL) contained 25 μL DNase I treated RNA solution, plus 8 μL 5× buffer (Cat. #05 893 151 001; Roche, Germany), 2 μL 20× reverse transcriptase (Cat. #05 893 151 001; Roche, Germany), and 5 μL double-distilled water. The temperature profile for the reverse transcription reaction (thermocycler: GenAmp 2700; Applied Biosystems, United States) was: primer annealing, 5 min at 25 °C; reverse transcription, 10 min at 55 °C; inactivation, 5 min at 85 °C; with cooling to 4 °C.

The primers used for the reverse transcription-quantitative PCR were either designed using an online tool (Primer-BLAST; NCBI) or predesigned primers (Assay Design Centre, Roche, Germany). The primer sequences, efficiencies, and product lengths are given in Supplementary Table 4. Among the tested candidate reference genes, those encoding beclin1 and dynactin subunit 2 showed the greatest expression stability in these samples and were used for normalization. The primer efficiencies were calculated based on validation experiments on two-fold and five-fold serial dilutions of cDNA derived from a mix of RNA from 10 suicide victims and 10 control subjects.

Quantitative PCR reactions were performed in 5 μL volumes in triplicate (ViiA7 real-time PCR system; Applied Biosystems, United States), as 0.75 μL cDNA sample, 1.15 μL double-distilled water, 2.5 μL SYBR Select Master Mix (Applied Biosystems, United States), and 0.6 μL of each forward and reverse primer (2.5 mM stock). The conditions were the same for all of the quantitative PCR cycling, except for annealing and extension. For the reference genes and for the *BDNF* transcripts, this followed: UDG activation, 2 min at 50 °C; polymerase activation, 10 min at 95 °C; denaturation, 15 s at 95 °C; with 40 cycles of annealing and extension for 1 min at 60 °C (beclin1, dynactin subunit 2, I-IX, IIc-IX) or 59 °C (IV-IX), or 40 cycles of annealing for 15 s at 59 °C with extension for 1 min at 72 °C (IXabcd); with all followed by the melting curve for 15 s at 95 °C, 1 min at 60 °C, and 15 s at 95 °C; and finally cooling to 4 °C.

Data analysis

BDNF methylation: After processing the raw sequencing data, quality filtering was applied. Due to an abundance of stretches of long homopolymeric regions, which are characteristic of bisulfite-converted DNA, the reads were quality filtered using bisulfite sequencing adjusted filter settings (Customer Support; Roche, Mannheim, Germany). In the read clean-up, adapter sequences were removed using the Cutadapt v1.11 software[33]. The reads were demultiplexed according to the study subjects (*i.e.* Multiplex Identifier_Forward#_ Multiplex Identifier_Reverse# combination) using the SFF tools and according to the *BDNF* ROIs, using the Cutadapt v1.11 software[33]. For sequence alignment, the FASTA format read files together with a file containing the bisulfite unconverted reference sequences were loaded into BiQ Analyzer HT[34] with the following settings: Minimal sequence identity, 0.80; minimal conversion rate, 0.85; and maximal fraction of unrecognized sites, 0.15. The results of the alignment were exported to MS Excel 2010, as the files containing numbers of loaded, filtered out, and exported reads. For each of the *BDNF* ROIs of each study, the following were determined: Subject mean conversion rate, mean methylation rate, and methylation status of individual CpGs in each read. Where the number of exported reads for a *BDNF* ROI of a subject was ≤ 20, the reads for the particular *BDNF* ROIs of this subject were excluded from any further analysis.

After testing for normal distributions of the data, the differences in the mean methylation levels of the *BDNF* ROIs, and the differences in the methylation frequencies of the individual CpGs for the ROIs between the suicide victims and the controls were determined using two-tailed Student's *t* tests for two independent samples. Statistical analysis and figure construction were carried out using the GraphPad Prism v6.0 software (GraphPad Software, United States). The Benjamini-Hochberg procedure[35] was implemented for correction for multiple comparisons, using a calculation file obtained online: BenjaminiHochberg.xlsx (https://github.com/abbiepopa/DPTB_RTOverallEG).

***BDNF* mRNA expression:** The expression of the *BDNF* transcripts was determined by the relative quantification method. The threshold cycle values were transformed into

mRNA quantities, taking efficiency into account. For each sample, the means of the triplicate measurements were calculated. Where the standard error within a triplicate was ≥ 20%, the replicate contributing the most to the standard error was excluded, and only the duplicate was considered for further analyses. Samples with standard errors within the triplicates of ≥ 40% were automatically excluded from further analyses. The experimental data were normalized to the geometric means of the quantities of beclin1 and dynactin subunit 2 mRNAs[36].

After testing the values obtained for normality of distribution, differences in *BDNF* transcript expression between control subjects and suicide victims were determined using two-tailed Student's *t* tests for two independent samples. The analyses were carried out using MS Excel 2010 and the GraphPad Prism v6.0 software (GraphPad Software, United States).

RESULTS

Study subjects

The ages and full background clinical data for the individual control subjects and suicide victims are given in Supplementary Table 5. Two-tailed Student *t* tests for independent samples showed significant differences in mean ages (± standard deviation) between the controls (54.6 ± 7.7 years) and suicide victims (44.0 ± 12.3 years), with the controls about 10 years older on average (P = 0.002). There were no significant differences in post-mortem intervals between these two study groups (28.2 ± 23.0 h *vs* 27.7 ± 13.8 h, P = 0.935).

The psychiatric diagnosis (where applicable) and post-mortem toxicology were obtained for each subject of both of the study groups. Among the control subjects, one had been previously diagnosed with schizophrenia and tested positive for psychoactive drugs and ethanol. One control subject without psychiatric diagnosis was also positive for psychoactive drugs, and six were positive for ethanol exclusively (Supplementary Table 5). Six suicide victims were previously diagnosed with one or more psychiatric disorders or symptoms, including: Schizophrenia, previous suicide attempt, depression disorder, bipolar disorder, adjustment disorder, anxiety, and alcohol dependence syndrome. Five of these suicide victims tested positive for psychoactive drugs, and two of them were positive for ethanol. The suicide victim with alcohol dependence syndrome was positive for ethanol. One suicide victim without psychiatric diagnosis was positive for psychoactive drugs. Eleven suicide victims were positive for ethanol exclusively.

BDNF methylation

The DNA methylation levels of the five *BDNF* regions for BA9, hippocampus, and blood of the control subjects and suicide victims were analyzed by targeted NGS of bisulfite-converted DNA. The mean bisulfite conversion rates and number of study subjects with sufficient numbers of reads in each of the studied tissues for each of the *BDNF* regions are given in Supplementary Table 6. Additionally, the number of reads for the post-filtration steps of each of the tissues studied are given in Supplementary Table 7.

Comparison of the control subjects and the suicide victims showed no significant differences in the methylation levels of the *BDNF* ROI (*i.e.* I1, I2, II, IV, VI) for both BA9 (Supplementary Figure 3) and hippocampus (Supplementary Figure 4, Table 1, and Supplementary Tables 8 and 9). In contrast, for blood of suicide victims compared to controls, there were significantly lower mean methylation levels for *BDNF* region I2 [t(40) = 2.832, P_{corr} = 0.01] (Figure 1 and Table 1). Closer inspection of the methylation within *BDNF* region I2 revealed significant differences for the methylation levels between the study groups for four of the CpGs. Compared to the controls, the suicide victims showed lower methylation of CpG 2 [t(40) = 3.044, P_{corr} = 0.011], CpG 6 [t(40) = 3.662, P_{corr} = 0.007], CpG 11 [t(40) = 2.923, P_{corr} = 0.014], and CpG 12 [t(40) = 3.921, P_{corr} = 0.004] (Figure 2 and Supplementary Table 10). However, there were no significant differences in the methylation levels for *BDNF* regions I1, II, IV, and VI in the blood of the controls and suicide victims (Supplementary Table 10).

BDNF mRNA expression

Expression levels of four transcripts from the *BDNF* locus in BA9, hippocampus, and blood were examined in control subjects and suicide victims by reverse transcription-quantitative PCR. The quality of the isolated RNA and mean quantification cycle

Table 1 Comparisons of the methylation levels across the *BDNF* regions in the control subjects and suicide victims

Tissue	Study group	*BDNF* region (% methylated)				
		I1	I2	II	IV	VI
Brain-BA9	C	4.55 ± 0.45	4.43 ± 0.39	8.48 ± 0.91	3.81 ± 0.32	3.37 ± 0.30
	SV	4.15 ± 0.56	4.28 ± 0.32	8.78 ± 1.09	4.03 ± 0.46	3.05 ± 0.23
	P value	0.260	0.557	0.667	0.418	0.090
Brain-Hippocampus	C	4.76 ± 0.48	4.16 ± 0.44	10.19 ± 0.51	3.74 ± 0.46	3.46 ± 0.34
	SV	4.40 ± 0.39	4.60 ± 0.43	10.30 ± 1.10	3.66 ± 0.37	3.52 ± 0.31
	P value	0.222	0.147	0.851	0.772	0.774
Blood	C	7.81 ± 1.03	6.83 ± 0.64	15.95 ± 1.36	5.71 ± 0.39	5.38 ± 0.95
	SV	7.00 ± 0.80	5.67 ± 0.57	14.26 ± 1.2	5.54 ± 0.38	4.80 ± 0.46
	P value	0.198	0.007[a]	0.067	0.521	0.245

[a]*P*corr < 0.05 (Benjamini–Hochberg method). The studied regions are labelled with Roman numerals (I, II, IV, and VI) according to the vicinity of the exons 1, 2, 4, or 6. The region preceding the first exon (I) is divided into two parts, I1 and I2 due to technical reason of maximum amplicon length recommendation for 454 GS Junior sequencing system (400 bp/region, including 454 GS Junior sequencing primers). Data are means ± 95% confidence interval. C: Controls; SV: Suicide victims. BA9: Brodmann area 9.

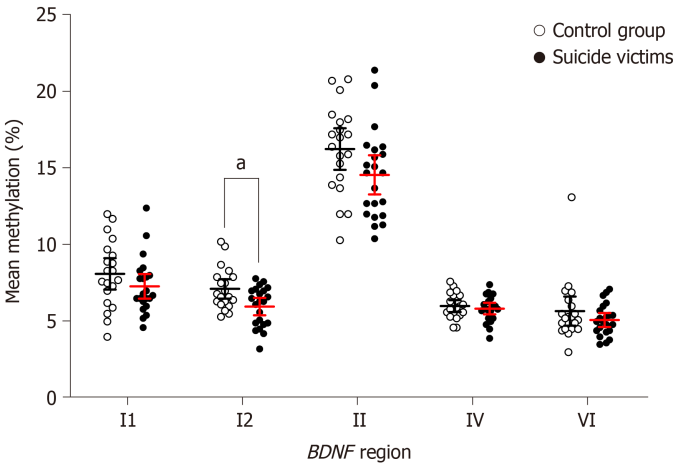


Figure 1 Methylation levels across the five studied *BDNF* regions in the blood from the control subjects and suicide victims. The studied regions are labelled with Roman numerals (I, II, IV, and VI) according to the vicinity of the exons 1, 2, 4, or 6. The region preceding the first exon (I) is divided into two parts, I1 and I2 due to technical reason of maximum amplicon length recommendation for 454 GS Junior sequencing system (400 bp/region, including 454 GS Junior sequencing primers). Each circle symbol represents an individual study subject. Data are medians (horizontal bars) of the mean methylation levels for the *BDNF* regions ± 95% confidence interval (red, suicide victims). [a]*P* < 0.05 (two-tailed Student's *t* test for two independent samples) between groups.

values for each condition are given in Supplementary Tables 11 and 12. In blood *BDNF* transcript expression analysis was not feasible due to extensive degradation of the RNA.

When compared to control subjects, the analysis for the brain region BA9 of the suicide victims showed slightly, but significantly, higher expression of the *BDNF* transcript NM_170731.4 [t(30) = 2.130, *P* = 0.042; 95% confidence interval: 0.001–0.054] (Figure 3 and Table 2). The analysis of the expression of other *BDNF* transcripts (*i.e.* NM_170732, NM_170733.3, NM_170735) in region BA9 showed no significant differences between study groups (Figure 3 and Table 2). In the hippocampus, none of the *BDNF* transcripts was significantly differentially expressed between the study groups (Supplementary Figure 5 and Table 2).

Table 2 *BDNF* alternative transcript expression in brain Brodmann area 9 and hippocampus in controls and suicide victims

Tissue	*BDNF* transcript	Total	Subjects				*P* value	95%CI
		Analyzed	Controls		Suicide victims			
		n (%)	*n* (%)	Relative expression	*n* (%)	Relative expression		
BA9	NM_170731.4	30	15	0.050 ± 0.013	15	0.077 ± 0.024	0.042[a]	0.001–0.054
	NM_170732.4	35	19	0.139 ± 0.026	16	0.154 ± 0.036	0.451	-0.026–0.058
	NM_170733.3	38	20	0.162 ± 0.027	18	0.188 ± 0.044	0.270	-0.022–0.075
	NM_170735	30	15	0.103 ± 0.019	15	0.095 ± 0.019	0.553	-0.033–0.018
Hippocampus	NM_170731.4	36	16	0.342 ± 0.117	20	0.312 ± 0.069	0.630	-0.154–0.094
	NM_170732.4	35	17	0.420 ± 0.120	18	0.369 ± 0.067	0.428	-0.181–0.079
	NM_170733.3	37	18	0.466 ± 0.111	19	0.475 ± 0.061	0.878	-0.111–0.129
	NM_170735	36	18	0.399 ± 0.092	18	0.341 ± 0.073	0.308	-0.171–0.056

[a]Nominal statistically significant difference ($P < 0.05$) two-tailed Student's *t* test for two independent samples. CI: Confidence interval. BA9: Brodmann area 9.

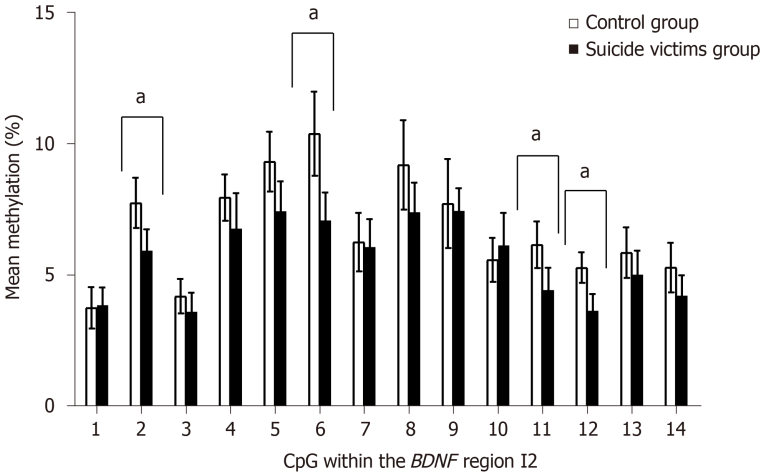


Figure 2 Methylation levels of individual CpGs within the *BDNF* I2 region in the blood from the control subjects and suicide victims. Data are means ± 95% confidence interval; [a]$P < 0.05$ (two-tailed Student's *t* test for two independent samples) between groups.

DISCUSSION

In this study, we examined *BDNF* methylation and the expression levels of *BDNF* transcripts in brain (*i.e.* BA9, hippocampus) and blood from control subjects and suicide victims from the Slovenian population, which is known to have a high risk of suicidality. Despite the decrease in Slovenian suicide rates in the past decade (SI-STAT Data Portal; Supplementary Figure 6), the number of deaths due to suicide still remains concerning. In Slovenia, roughly 80% of suicide victims are men, and the most commonly used suicide method is suffocation by hanging[37].

Study subjects

To maximize the homogeneity of our study groups, tissue samples were collected only from male controls who died by acute cardiac arrest (age range: 33-64 years) and from male suicide victims who died by hanging (age range: 29-60 years). The difference in the mean ages between the study groups was not unexpected (controls were 10.6 years older), as the control group was represented by subjects who passed away due to a reason more commonly associated with an older population. Due to the small sample size, the suicide victims were not subgrouped in terms of their comorbidities and/or medications.

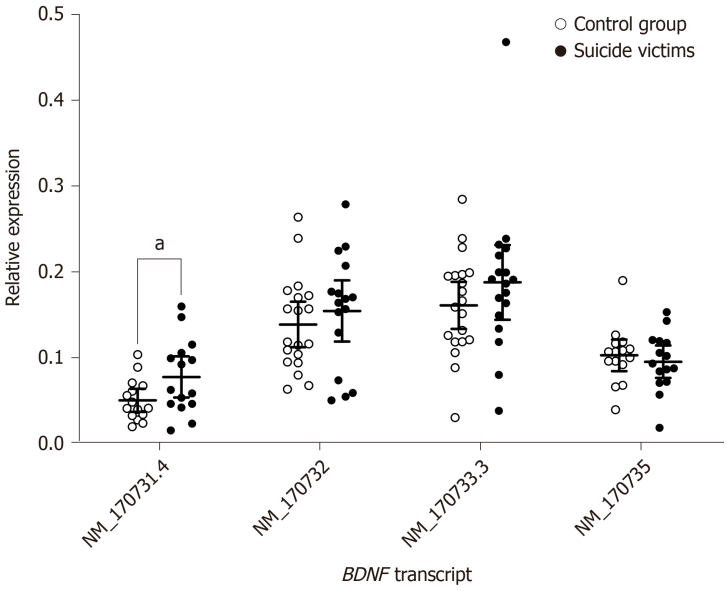


Figure 3 Relative expression levels of alternative *BDNF* transcripts in the Brodmann area 9 brain region of the control subjects and suicide victims. Each circle symbol represents an individual study subject. Data are medians (horizontal bars) of the mean methylation levels for the *BDNF* regions ± 95% confidence interval (black, suicide victims). [a]*P* < 0.05 (two-tailed Student's *t* test for two independent samples) between groups.

BDNF methylation

NGS of bisulfite-converted DNA was used to determine the methylation rates across the five *BDNF* regions, plus the methylation rates of individual CpGs within these regions. Methylation was assayed for the BA9 of the prefrontal cortex, the hippocampus, and blood and compared between controls and suicide victims.

For BA9 and hippocampus, the present study did not show any significant differences in *BDNF* methylation between the controls and suicide victims. Our previous whole-genome methylation study showed several differentially methylated CpGs in BA9 and hippocampus of suicide victims compared to controls[28]. However, none of these differentially methylated CpGs was located within or in the vicinity of the *BDNF* locus, which is in agreement with the present study. In contrast, other studies have shown increased *BDNF* locus methylation in brains of suicide victims[14,27], although they explored different brain areas, which would explain these discrepancies.

Comparison of the *BDNF* locus methylation for blood of the controls and suicide victims instead showed *BDNF* I2 (upstream of exon I) with significantly reduced methylation for suicide victims. Also, more specifically within *BDNF* I2, 4 of the 14 CpGs examined were significantly hypomethylated in blood of these suicide victims. We have been unable to find similar studies to date that have the *BDNF* methylation of DNA from blood in completed suicides. Previous studies on blood from elderly people and patients with psychiatric or other conditions who also showed suicidal behavior (*i.e.* suicide ideation, suicide attempts) have reported increased *BDNF* methylation over the controls[21-25]. To the best of our knowledge, there are only two studies to date that have reported decreased *BDNF* methylation in blood of psychiatric patients compared to controls. However, in these two studies, none of the subjects showed suicidal behavior[19,26].

BDNF mRNA expression

Quantitative PCR was used to determine the expression levels of four alternative *BDNF* transcripts in brain tissue (BA9, hippocampus) and blood of these controls and suicide victims: NM_170731.4, NM_170732, NM_170733.3, and NM_170735.

In BA9, relative to the controls, the *BDNF* transcript NM_170731.4 (5′-exon = exon I) showed slightly, but significantly, higher expression in the suicide victims. With regard to psychiatric disorders, there are only two studies to date that have examined expression of some of the individual *BDNF* mRNA transcripts[30,31]. Wong *et al*[30] showed higher expression of *BDNF* transcript I-IX (5′-exon = exon I) compared to control subjects in dorsolateral prefrontal cortex in patients with schizophrenia who died by suicide. However, as almost half of their schizophrenia suicide victims tested positive for antidepressants, the authors could not rule out effects of the drugs on the

experimental outcome[30]. Reinhart *et al*[31] revealed higher expression over controls for transcript IIc-IX (5'-exon = exon IIc) in striatum of subjects with major depressive disorder. Their patient groups (*i.e.* schizophrenia, bipolar disorder, major depressive disorder) also included subjects who died by suicide (approximately 40 %). Interestingly, the total *BDNF* mRNA levels did not differ in any of these disease states compared to controls in any of the brain regions they studied (*i.e.* dorsolateral prefrontal cortex, striatum, hippocampus)[31].

In the present study, determination of the expression of these *BDNF* transcripts in blood could not be carried out. As shown in Supplementary Table 11, blood RNA was significantly degraded as reflected in the low RNA integrity numbers. Low quality RNA was further indicated by high quantification cycles for the reference genes in comparison to the brain tissue (Supplementary Table 12). It should be noted that the brain and blood tissue samples were frozen at -80 °C, and the nucleic acids were not immediately extracted from the tissues. Freezing and thawing of blood samples causes extensive cell lysis, which leads to poor RNA recovery, while brain tissue can be frozen and thawed without significant effects on RNA recovery[38].

Nonetheless, a number of past studies that explored total *BDNF* mRNA levels have shown decreased expression in the postmortem brain of suicide victims and in blood of psychiatric patients that attempted suicide[14,15,17,18,39].

Limitations

Several limitations of this study can be noted. First, the sample size was relatively small (n = 42), which limits the power of the study. Moreover, only tissue samples from males were collected. Therefore, the results might not be generalizable to the wider (female) population. Further, for the group of suicide victims, the lack of subgrouping, the exclusion of subjects with comorbid psychiatric disorders, and the use of psychoactive drugs might represent confounding factors.

A hypothesis-driven approach was used here, which focused on one candidate gene. Psychiatric disorders, and also suicide and related behaviors, are multifactorial disorders with numerous interacting genetic and environmental risk factors involved. However, the choice to study the *BDNF* gene was based on previous studies that had implicated its involvement in the pathogenesis of psychiatric disorders, including suicide.

Considering the DNA methylation approach used, despite preservation of the methylation patterns during bisulfite treatment of DNA, this reaction does not discriminate between methylation and hydroxymethylation of cytosines. Indeed, recent studies that have used oxidative bisulfite NGS have shown altered gene hydroxymethylation patterns in the brain of depressed patients who died by suicide [40,41]. DNA methylation and gene expression are not only tissue specific but also cell type specific. Thus, for the brain analysis, the tissue here included several cell types of particular brain regions (*i.e.* within BA9 and hippocampus). Hence, the data obtained from the brain tissues represent *BDNF* methylation and *BDNF* mRNA expression across all cell types from these brain regions. We also did not explore total *BDNF* mRNA expression in the present study sample. Finally, due to substantial RNA degradation, we were not able to obtain data on *BDNF* transcript expression in blood of these control subjects and suicide victims.

CONCLUSION

To the best of our knowledge, this is the first study that aimed at exploring *BDNF* locus methylation and the expression of four *BDNF* transcripts in brain and peripheral blood in the same cohorts. This was also carried out in a population with a high suicide rate. Despite this, *BDNF* methylation analysis of the brain tissues did not show differences between the study groups. The higher observed expression of *BDNF* transcript I-IX in BA9 of the suicide victims should be taken with caution, as this barely reached statistical significance. However, the data obtained from blood are interesting, especially in terms of the direction of the effects, although due to the extensively degraded blood RNA we were not able to confirm these effects on mRNA expression. Finally, although the present study and data from a number of other studies implicate *BDNF* in suicidality, it must be kept in mind that suicide is a multifactorial disorder with numerous environmental and genetic risk factors involved.

ARTICLE HIGHLIGHTS

Research background

Suicidal behavior is a complex behavior with multifactorial etiology. Despite the large body of work, the full mechanism of suicidal behavior is not known. There are however strong indicators that changes in epigenetic mechanisms, specifically DNA methylation, can be an important factor.

Research motivation

Brain derived neurotrophic factor, *BDNF*, plays an important role in brain plasticity, and therefore it could be involved in modulation of suicidal behavior. Molecular-genetic data from a population with a high suicide rate could contribute to deeper understanding of the biological background of suicide.

Research objectives

The objective of our study was to investigate *BDNF* at two levels: DNA methylation and gene expression. As DNA methylation and gene expression can be highly tissue specific, we included two different brain regions and also blood as a peripheral tissue that is more easily accessible.

Research methods

Altogether, 42 subjects were included in the study (20 control subjects and 22 suicide victims). Samples of brain (hippocampus and Brodmann area 9) and blood were obtained during routine autopsy. We used targeted bisulfite sequencing to assess the DNA methylation level of five *BDNF* regions of interest (I1, I2, II, IV, and VI), and quantitative PCR to determine gene expression of four *BDNF* transcripts.

Research results

When comparing suicide victims and control group, we observed no significant changes in *BDNF* DNA methylation level in the brain. Changes were observed in blood, where suicide victims exhibited lower mean DNA methylation level of *BDNF* region I2 compared to the control group. In gene expression analysis, one *BDNF* transcript (NM_170731.4.) was upregulated in Brodmann area 9 of suicide victims compared to the control group.

Research conclusions

Due to tissue associated limitation, a complete insight into *BDNF* changes was not possible, namely inspection of blood *BDNF* expression level. Still, we observed changes both in DNA methylation level in blood and gene expression in brain, indicating the possible association of *BDNF* with suicidal behavior.

Research perspectives

Data from this study was obtained from a Slovenian population, which has a high suicide risk. The findings are thus an important contribution to a better understanding of the biological basis of suicidal behavior and the involvement of neurotrophic factors such as *BDNF*.

ACKNOWLEDGEMENTS

The authors would like to thank the Institute of Forensic Medicine in the Faculty of Medicine of the University of Ljubljana, Slovenia for long term collaboration, and to Ms. Anka Hotko for assistance in DNA isolation and bisulfite conversion. The authors would like to thank Dr. Christopher Berrie and Dr. John Hancock for critical appraisal and scientific English editing of the manuscript.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1314-1327

DOI: 10.5498/wjp.v11.i12.1314

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

Developing a nomogram for predicting the depression of senior citizens living alone while focusing on perceived social support

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Author contributions: Byeon H was designed the study, involved in data interpretation, preformed the statistical analysis, and assisted with writing the article.

Institutional review board statement: The study was approved by the Research Ethics Review Board of the National Biobank of Korea (No. KBN-2019-005) and the H University (No. 20180042).

Informed consent statement: All patients gave informed consent.

Conflict-of-interest statement: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Data sharing statement: Technical appendix, statistical code from the corresponding author at bhwpuma@naver.com.

STROBE statement: The authors have read the STROBE statement—checklist of items, and the manuscript was prepared and revised according to the STROBE statement—checklist of items.

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Abstract

BACKGROUND

Although the number of senior citizens living alone is increasing, only a few studies have identified factors related to the depression characteristics of senior citizens living alone by using epidemiological survey data that can represent a population group.

AIM

To evaluate prediction performance by building models for predicting the depression of senior citizens living alone that included subjective social isolation and perceived social support as well as personal characteristics such as age and drinking.

METHODS

This study analyzed 1558 senior citizens (695 males and 863 females) who were 60 years or older and completed an epidemiological survey representing the South Korean population. Depression, an outcome variable, was measured using the short form of the Korean version CES-D (short form of CES-D).

RESULTS

The prevalence of depression among the senior citizens living alone was 7.7%. The results of multiple logistic regression analysis showed that the experience of suicidal urge over the past year, subjective satisfaction with help from neighbors, subjective loneliness, age, and self-esteem were significantly related to the depression of senior citizens living alone ($P < 0.05$). The results of 10-fold cross validation showed that the area under the curve of the nomogram was 0.96, and the F1 score of it was 0.97.

CONCLUSION

It is necessary to strengthen the social network of senior citizens living alone with friends and neighbors based on the results of this study to protect them from

Supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2018R1D1A1B07041091, NRF-2021S1A5A8062526).

Country/Territory of origin: South Korea

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Received: May 23, 2021
Peer-review started: May 23, 2021
First decision: July 14, 2021
Revised: July 18, 2021
Accepted: November 3, 2021
Article in press: November 3, 2021
Published online: December 19, 2021

P-Reviewer: Wang Z
S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

depression.

Key Words: Senior citizens living alone; Nomogram; Depression; Risk factor; Perceived social support; Subjective social isolation

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Core Tip: In this study, the significant predictors of depression of the senior citizens living alone were the experiences of suicidal urge over the past year, dissatisfaction with help from neighbors, subjective loneliness, age, and low self-esteem. The results of this study implied that it is necessary to develop a support system customized for subjects to strengthen the relation network for preventing depression in senior citizens living alone so that they can receive actual support (reinforced qualitative network) from acquaintances such as neighbors rather than the frequency of physical contact (reinforced quantitative network).

Citation: Byeon H. Developing a nomogram for predicting the depression of senior citizens living alone while focusing on perceived social support. *World J Psychiatr* 2021; 11(12): 1314-1327
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1314.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1314

INTRODUCTION

The incidence of diseases involving senile dementia is rapidly increasing globally due to a rapid increase in the aging population[1]. One of the outcomes of these diseases, depression, is an important and frequent psychiatric disorder in the senile stage, and it is predicted to become the second most important factor in the global disease burden [1]. Since depression can be treated through drug and psychosocial therapy, it is very important to diagnose and treat it as soon as possible. Nevertheless, it is difficult to diagnose depression in the senile stage in good time because it is often erroneously confused with physical symptoms (*e.g.*, a headache, dizziness, *etc.*) by other family members (senior citizens complain about these more often than younger people), while cognitive decline due to depression is often obscured by the normal aging process[2,3]. Thus, it tends to be neglected without receiving appropriate attention, diagnosis, and/or treatment[2,3]. Hence, many senior citizens living in the community may be suffering from depression even if they have not been clinically diagnosed with it by medical personnel[4].

Although detecting depression in good time is an important requirement for the aged, depression tends to be discovered late or not treated adequately due to various reasons, such as a lack of awareness of one's depression, the complex manifestation of depression, and a decrease in the interest of close acquaintances and family members. However, if geriatric depression is neglected without being properly treated, the individual will suffer from unnecessary mental and social pain, which can lead to serious outcomes such as suicidal ideation[5,6]. Consequently, it is very important to accurately diagnose and detect geriatric depression when treating diseases involving senility[5,6].

The proportion of the elderly population who are living with and/or supported by their children continues to decrease in South Korea in concert with a rapid increase in the number of elderly people living alone[7]. As of 2015, the number of senior citizens living alone in South Korea was 1379000, which is a 1.8-fold increase (777000 people) compared to 2005[7], and is expected to increase to 3.43 million by 2035[7]. Moreover, the proportion of senior citizens living alone is expected to increase to 23.2% in 2035 from 17.8% in 2020. Senior citizens living alone must handle everything that arises in their daily lives, and they exist in poorer environments than those supported by their children not only from economic (income and consumption) and welfare perspectives but also concerning their mental health. The findings from the Survey of Living Conditions and Welfare Needs of Korean Older Persons[7] show that senior citizens living alone are usually old and poorly educated, while the proportion of female senior

citizens living alone is five times higher than those living with their families. Pogŏn Sahoe Yŏn'gu[8] reported that senior citizens living alone had poorer subjective health and were more likely to suffer from a disease such as depression than those living with their families. Thus, the mental health of senior citizens living alone is poorer than those living with their families and the causes of depression in the former are many rather than singular[8,9].

Although the number of senior citizens living alone is increasing, few researchers have identified factors related to the characteristics of depression in these individuals by using epidemiological survey data representative of this population group. Although epidemiological surveys on the prevalence of depression in the senile stage have been actively conducted in many countries[10-13], the prevalence of depression varied between them due to differences in the survey sampling methods, depression testing tools, and evaluation methodology. Researchers usually use two-phase designs in psychiatric epidemiological studies to classify subjects into a depression-positive group and a depression-negative group quickly and economically by using a simple standardized screening test in the first phase followed by conducting a robust diagnostic test in the second phase to save on the labor and economic burden[14]. There-fore, in the first phase, we used the Center for Epidemiological Studies Depression Scale (CES-D)[15], a widely used standardized screening test, to identify the prevalence of depression in senior citizens living alone. Second, we evaluated the prediction performance [area under the curve (AUC) for the receiver operating characteristic, general accuracy, balanced accuracy, F1 score, sensitivity, and specificity] by building models for predicting depression in senior citizens living alone, which included subjective social isolation and perceived social support as well as personal characteristics such as age and alcohol consumption. Last, we developed a nomogram that allows practitioners to check multiple risk factors for depression in senior citizens living alone using visual graphs and to calculate the prevalence of depression while considering the personal characteristics of the subjects based on these results.

MATERIALS AND METHODS

Data source

This study is a secondary data based on the Korean Psychosocial Anxiety (KPA) survey, an epidemiological survey representing the South Korean population. KPA-survey was conducted from August to September 2015 by the Korea Institute for Health and Social Affairs. The study stratified the population, obtained from the Residence Registration Data (complete enumeration) conducted by the Ministry of Security and Public Administration as of June 2015, into 17 cities and provinces (*i.e.*, Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan, Sejong, Gyeonggi-do, Gangwon-do, Chungcheongbuk-do, Chungcheongnam-do, Jeollabuk-do, Jeollanam-do, Gyeongsangbuk-do, Gyeongsangnam-do, and Jeju-do). Afterward, this study extracted samples using the quota sampling method with considering the gender, age, and residential area ratios. This study selected 200 eups, myeons, and dongs from 3552 eups, myeons, and dongs in South Korea using the probabilities proportional to size (PPS) method. In order to secure randomness when extracting sampling sites, the PPS was applied after sorting the districts in the order of city, county, and district based on the administrative district code. After selecting 200 sampling sites, the 5th household from the Community Service Center of each selected eup, myeon, or dong was chosen as the sampling household by visiting the selected sampling site, and finally, 7000 adults (19 years or older) were surveyed. This study conducted an in-person survey by having trained surveyors who received survey training visit the sample households using the computer assisted personal interview method. This study was approved by H University's Clinical Research Ethics Committee (No. 20180042). This study analyzed 1558 senior citizens (695 males and 863 females) who were 60 years or older and completed the KPA-survey.

Measurement

Depression, an outcome variable, was measured using the short form of the Korean version CES-D (short form of CES-D)[16]. CES-D[15] is a standardized self-report depression test that is used most commonly in the world and can measure depression in healthy people easily. This test was developed by the National Institute of Mental Health for investigating the epidemiological status of depression in a community and has been widely used in many countries in various languages as a screening instrument for depression[16]. Many previous studies have proven the high internal

consistency and validity of CES-D[17,18]. More recently, the scale of short form of CES-D, which has secured good reliability and validity, has also been developed and used for subjects who have difficulties in responding to the 20 items of the original CES-D (*e.g.*, senior citizens, those with dyslexia, or illiterates)[19-23]. Short form of CES-D has been continuously used in epidemiological surveys because it reduces the response burden of the participants and it has the advantage that it can be easily used for the elderly who suffer from many physical symptoms and have difficulties in answering a long item due to a decrease in concentration[24]. The KPA-survey, the data source of this study, used standardized short form CES-D consisting of 11 items. This test classified depression into four levels based on the frequency of depression symptoms experienced by the subject over the past week. Moreover, the severity of symptoms was classified into four classes using a Likert scale (0 points = rare or 1 d or fewer per week; 1 point = occasional or 1 to 2 d per week; 2 points = often or 3 to 4 d per week; and 3 points = mostly or 5 d or more per week). A higher total score means more depression symptoms. This study defined the threshold of depression as 16 points based on the previous study[22] on the elderly in South Korea.

Explanatory variables were age (continuous variable), alcohol consumption (abstainers or normal drinkers, high-risk drinkers, and those with alcohol use disorder), self-esteem, suicidal ideation over the past year (yes or no), subjective social isolation (rarely, occasionally, often, or usually lonely), frequency of communication with other family members (a 10-point scale with a higher score infers more frequent communication), interaction with neighbors and friends [regular club activities (yes or no), perceived social support (a 10-point scale), trust neighbors (yes or no), and satisfied with help (support) from neighbors (yes or no)], satisfaction with the neighborhood environment (yes or no), satisfaction with the safety level of the neighborhood (yes or no), and satisfaction with the medical services in the region (yes or no) [25]. The self-esteem item was measured by using the Self-Esteem Scale (SES) comprising 10 items (a total score of 40 points)[26]: A low score (15 or less) indicates poor self-esteem. The Alcohol Use Disorders Identification Test (AUDIT)[27] developed by the World Health Organization for the preliminarily screening of high-risk drinkers comprises 10 items with a total score of 40 points: 0-15 points identify abstainers and normal drinkers, 16-19 points identify high-risk drinkers, and ≥ 20 points identify individuals with alcohol use disorder.

Developing a model to predict the depression of senior citizens living alone

The general characteristics and depression prevalence of the subjects were presented/present in percentages. The effects of depression were examined by Chi-square test. This study built a depression prediction model using logistic regression analysis to find out the effect of each variable on depression. This study selected variables using step-forward regression analysis. Moreover, this study presented an unadjusted crude model, which was not adjusted with confounding factors, and an adjusted model, which was adjusted with confounding factors.

The developed depression prediction model contained a nomogram to make it possible for clinicians to interpret the prediction results (prediction probability) easily. The nomogram was composed of 4 elements. The first was a point line. It was the line located at the top of the monogram to indicate the score corresponding to the risk range of a factor. In the case of a logistic nomogram, it ranged from 0 to 100 points. The second was a risk factor line. This line indicates the score range of a risk factor influencing the occurrence of an event. The number of risk factor lines was equal to the number of risk factors. The third was a probability line. The probability line was the sum of finally calculated nomogram scores and it was placed at the bottom of the nomogram to derive the probability (risk) of depression. The fourth is a total point line. It was constructed by calculating it based on a statistical model.

Evaluating the prediction performance of a model for predicting the depression of senior citizens living alone

The sample size of this study was small (n = 1558). Therefore, when the prediction performance of the model is validated using a held-out validation method (*i.e.*, a validation method that divides the dataset into a training dataset and a validation dataset at a 7:3 ratio), it poses a risk of overfitting. Consequently, it is more likely to decrease the reliability of prediction results. As a result, this study used 10-fold cross-validation to validate the prediction performance of the developed depression prediction model (nomogram). AUC, general accuracy, balanced accuracy, F1 score, sensitivity, specificity and calibration plot were presented. The calibration plot is a graph for visually confirming the degree of agreement (y, Calibration curve and x,

predicted probability) between the predicted probability and the observed probability. Sensitivity indicates the ratio of true positives: The ratio of the developed model to predict the senior citizen living alone with depression as depression. Specificity indicates the ratio of true negatives: The ratio of the developed model to predict the senior citizen living alone without depression as no-depression accurately. R version 4.0.3 (Foundation for Statistical Computing, Vienna, Austria) was used for analyses and significance level was 0.05 in two-tailed test.

RESULTS

General characteristics of subjects

General characteristics of all subjects (1558 subjects) are presented in Table 1. The mean age was 67.9 ± 5.5 years old: 55.4% of them were women and 44.6% of them were men. The results of the AUDIT showed that most of the subjects were normal (52.4%), no suicidal urge over the past one year (91.0%), very rare subjective loneliness (44.1%), and homemaker (35.5%). The prevalence of depression among the senior citizens living alone in the community, measured by short form of CES-D was 7.7%.

Characteristics of the subject according to the prevalence of depression

The characteristics of the subjects according to the prevalence of depression are presented in Table 2. The results of chi-square test showed that depression was significantly ($P < 0.05$) affected by age, self-esteem, subjective frequency of communication with other family members, alcohol use disorder, the experience of suicidal urge over the past year, subjective trust satisfaction with neighbors, subjective satisfaction with help (support) from neighbors, subjective satisfaction of the safety level of the neighborhood, subjective satisfaction of the medical service of the region, regular club activities, and subjective loneliness.

Developing a model for predicting depression of senior citizens living alone

Table 3 shows a model for predicting the depression of senior citizens living alone. The results of univariate logistic regression analysis (crude model) showed that all variables (age, self-esteem, alcohol use disorder, the experience of suicidal urge over the past year, subjective trust satisfaction with neighbors, subjective satisfaction of the living environment of the neighborhood, subjective satisfaction of the safety level of the neighborhood, subjective satisfaction of the medical service of the region, regular club activities, subjective loneliness, subjective frequency of communication with other family members, and subjective frequency of communication with neighbors/friends) were significantly ($P < 0.05$) related to the depression of senior citizens living alone. However, the results of the adjusted model revealed that the depression of senior citizens living alone was independently associated only with the experience of suicidal urge over the past year [odds ratio (OR): 3.57, 95% cumulative incidence (CI): 1.55-8.22], subjective satisfaction with help (support) from neighbors (OR: 0.29, 95%CI: 0.13-0.66), subjective loneliness (occasionally lonely: OR: 5.04, 95%CI: 1.00-4.65; often lonely: OR: 187.19, 95%CI: 23.17-1512.13; mostly lonely: OR: 758.12, 95%CI: 56.44-10183.32), age (OR: 1.17, 95%CI: 1.07-1.26), and self-esteem (OR: 0.81, 95%CI: 0.72-0.91).

Developing a nomogram to predict the depression of senior citizens living alone based on multiple risk factors

A nomogram for predicting the depression of elderly living alone based on multiple risk factors is presented in Figure 1. Among the risk factors of depression of senior citizens living alone, subjective loneliness had the greatest influence, and the senior citizens living alone who responded that they felt lonely showed the highest risk of depression. For example, the nomogram for predicting depression predicted that the depression risk of senior citizens who had suicidal urge over the past year, were not satisfied with subjective help (support) with neighbors, thought that they were mostly lonely, had 15 points in Rosenburg SES scale (self-esteem), and were 80 years or older was 99.8% (Figure 2).

Validating a nomogram for predicting the depression of senior citizens living alone

The developed nomogram for predicting the depression of senior citizens living alone was validated by using AUC, general accuracy, balanced accuracy, F1 score, sensitivity, and specificity (Table 4). The results of 10-fold cross validation showed that the AUC of the nomogram was 0.96, the general accuracy of it was 0.95, the balanced

Table 1 General characteristics of subjects

Characteristics	*n* (%)
Age, mean ± SD	67.9 ± 5.5
Gender	
Male	695 (44.6)
Female	863 (55.4)
Occupation (ISCO)	
Managers	20 (1.3)
Professional	12 (0.8)
Clerical support workers	6 (0.4)
Service workers	97 (6.2)
Sales workers	166 (10.7)
Skilled agricultural, forestry and fishery workers	88 (5.6)
Craft and related trades workers	77 (4.9)
Plant and machine operators, and assemblers	9 (0.6)
Elementary occupations	130 (8.3)
Housewives	553 (35.5)
Unemployed persons	399 (25.6)
Alcohol use disorder (AUDIT)	
Normal drinker	817 (52.4)
High-risk drinker	278 (17.8)
Alcohol use disorder	13 (0.8)
Self-esteem, the experience of suicidal urge over the past year	
No	1418 (91.0)
Yes	140 (9.0)
Subjective loneliness	
Very rare	687 (44.1)
Occasionally lonely	639 (41.0)
Often lonely	210 (13.5)
Mostly lonely	22 (1.4)
Self-esteem scale, mean ± SD	28.7 ± 3.4
Depression	
No	1438 (92.3)
Yes	120 (7.7)

ISCO: International Standard Classification of Occupations; ADUIT: Alcohol Use Disorders Identification Test.

accuracy of it was 0.80, the sensitivity of it was 0.98, the specificity of it was 0.62, and the F1 score of it was 0.97. The equation of the calibration plot was drawn along the ideal line; coefficient of determination (R squre) was 0.853 (Figure 3). The AUC of the developed nomogram for predicting the depression of senior citizens living alone is presented in Figure 4.

Table 2 The characteristics of the subjects according to the prevalence of depression, *n* (%)

Variables	Depression		*P*
	No (*n* = 1438)	Yes (*n* = 120)	
Age, mean ± SD	67.75 ± 5.53	70.95 ± 4.99	< 0.0001
Self-esteem scale, mean ± SD	29.06 ± 3.26	25.01 ± 3.43	< 0.0001
Subjective frequency of communication with other family members, mean ± SD	2.54 ± 0.95	2.05 ± 0.94	< 0.0001
Subjective frequency of communication with neighbors and friends, mean ± SD	2.25 ± 1.05	2.05 ± 1.11	0.05
Alcohol use disorder			< 0.001
Normal drinker	766 (93.8)	51 (6.2)	
High-risk drinker	258 (92.8)	20 (7.2)	
Alcohol use disorder	6 (46.2)	7 (53.8)	
Self-esteem, the experience of suicidal urge over the past year			< 0.001
No	1349 (95.1)	69 (4.9)	
Yes	89 (63.6)	51 (36.4)	
Subjective trust satisfaction with neighbors			< 0.001
No	163 (76.9)	49 (23.1)	
Yes	1275 (94.7)	71 (5.3)	
Subjective satisfaction with help from neighbors			< 0.001
No	420 (85.7)	70 (14.3)	
Yes	1018 (95.3)	50 (4.7)	
Subjective satisfaction of the living environment of the neighborhood			0.08
No	245 (89.7)	28 (10.3)	
Yes	1193 (92.8)	92 (7.2)	
Subjective satisfaction of the safety level of the neighborhood			< 0.001
No	230 (84.3)	43 (15.7)	
Yes	1208(94.0)	77 (6.0)	
Subjective satisfaction of the medical service of the region			< 0.001
No	386 (88.5)	50 (11.5)	
Yes	1,438 (92.3)	120(7.7)	
Regular club activities			< 0.001
No	975 (90.5)	103(9.5)	
Yes	463 (96.5)	17(3.5)	
Subjective loneliness			< 0.001
Very rare	685 (99.7)	2 (0.3)	
Occasionally lonely	617 (96.6)	22 (3.44)	
Often lonely	131 (62.4)	79(37.6)	
Mostly lonely	5 (22.7)	17(77.3)	

DISCUSSION

The prevalence of depression in senior citizens living alone in the community measured using the short form of the CES-D was 7.7%, which is 2-4 times higher than reported in previous studies (1%-4%)[28-31]. In particular, after combining the results from 16 studies, Beekman *et al*[32] reported that the weighted mean prevalence of depression in the elderly living alone in the community was 1.77%. In contrast, Park *et al*[33] identified the prevalence of depression in 6018 senior citizens who participated

Table 3 A model for predicting the depression of senior citizens living alone: Odds ratio and 95% confidence interval

Variables	Crude model	Adjusted model	VIF
Alcohol use disorder			
Normal drinker	1.00	1.00	
High-risk drinker	1.16 (0.68, 1.99)	1.08 (0.45, 2.59)	1.14
Alcohol use disorder	17.52 (5.67, 54.06)[a]	1.54 (0.16, 14.80)	1.20
Self-esteem, the experience of suicidal urge over the past year			
No (Ref)			
Yes	12.83 (7.74, 21.26)[a]	3.57 (1.55, 8.22)[a]	1.27
Subjective trust satisfaction with neighbors			
No (Ref)	1.00	1.00	
Yes	0.20 (0.12, 0.32)[a]	1.02 (0.43, 2.40)	1.37
Subjective satisfaction with help from neighbors			
No (Ref)	1.00	1.00	
Yes	0.24 (0.15, 0.39)[a]	0.29 (0.13, 0.66)[a]	1.40
Subjective satisfaction of the living environment of the neighborhood			
No (Ref)	1.00	1.00	
Yes	0.41 (0.25, 0.66)[a]	0.51 (0.23, 1.10)	1.19
Subjective satisfaction of the safety level of the neighborhood			
No (Ref)	1.00	1.00	
Yes	0.32 (0.20, 0.53)[a]	0.46 (0.21, 1.04)	1.19
Subjective satisfaction of the medical service of the region			
No (Ref)	1.00	1.00	
Yes	0.46 (0.28, 0.73)[a]	0.56 (0.26, 1.20)	1.19
Regular club activities			
No (Ref)	1.00	1.00	
Yes	0.38 (0.20, 0.70)[a]	2.04 (0.81, 5.15)	1.31
Subjective loneliness			
Very rare (Ref)	1.00	1.00	
Occasionally lonely	12.21 (2.86, 52.14)[a]	5.04 (0.58, 43.39)	6.87
Often lonely	206.54 (50.13, 850.86)[a]	187.19 (23.17, 1512.13)[a]	7.89
Mostly lonely	1164.50 (210.83, 6431.88)[a]	758.12 (56.44, 10183.32)[a]	3.10
Subjective frequency of communication with other family members	0.55 (0.49, 0.61)[a]	0.95 (0.71, 1.27)	2.16
Subjective frequency of communication with neighbors and friends	0.59 (0.53, 0.66)[a]	1.10 (0.81, 1.48)	2.12
Age	0.89 (0.85, 0.93)[a]	1.17 (1.07, 1.26)[a]	1.42
Self-esteem scale	0.70 (0.65, 0.74)[a]	0.81 (0.72, 0.91)[a]	1.33

[a]$P < 0.05$.
VIF: Variance Inflation Factor.

in the Nationwide survey on dementia in Korea that was 17.5% higher than in the present study. The differences in the reported prevalence of depression suggest that the number of senior citizens at a high risk of depression (even if not yet clinically diagnosed) may actually be higher than the reported number. Therefore, the development of a customized prediction model that can screen this high risk of de-pression group based on the results of the present study is needed.

Table 4 Validating a nomogram for predicting the depression of senior citizens living alone

Measure	Description	Value
TP		1012
TN		49
FP		29
FN		18
AUC		0.96
Accuracy	(TP + TN)/(TP + TN + FP + FN)	0.95
Balanced accuracy	[TP/(TP + FN) + TN/(TN + FP)]/2	0.80
Sens	TP/(TP + FN)	0.98
Spec	TN/(TN + FP)	0.62
FPR	FP/(TN + FP)	0.37
FNR	FN/(TP + FN)	0.01
F1 score	2/(1/Sens + 1/PPV)	0.97

TP: True positive; TN: True negative; FP: False positive; FN: False negative; AUC: Area under the curve; FPR: False positive rate; FNR: False negative rate; PPV: Potential path volume; Sens: Sensitivity; Spec: Specificity.

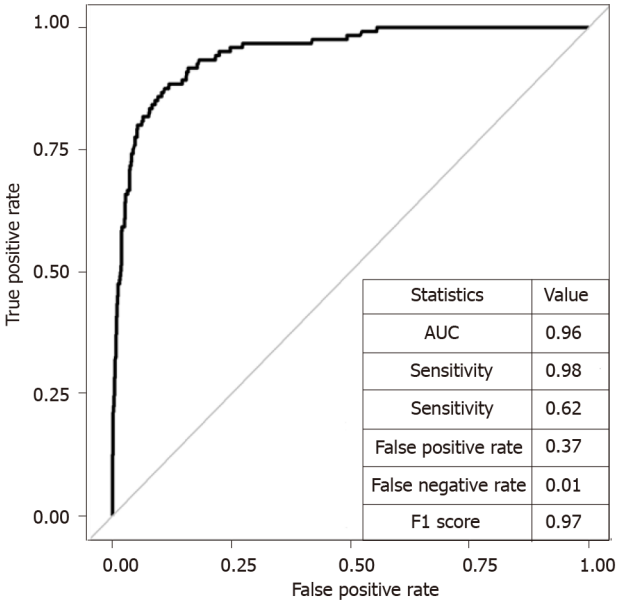


Figure 1 The area under the curve of the developed nomogram for predicting the depression of senior citizens living alone. AUC: Area under the curve.

In the present study, the significant predictors of depression in senior citizens living alone were suicidal ideation over the past year, dissatisfaction with help (support) from neighbors, subjective loneliness, age, and low self-esteem. It is known that the prevalence of depression in the elderly increases with age[34,35] and low self-esteem [36,37]. Many studies have reported that old people show a high risk of depression regardless of gender because they are more likely to lose their spouses, become physically weaker, have fewer opportunities to participate in social activities, become more susceptible to disease, and suffer from physical dysfunction[38,39]. Nevertheless, researchers have mainly tried to identify individual risk factors for depression using regression analysis[40-43], which negates discovering multiple risk factors for depression. In the present epidemiologic study, multiple risk factors for depression in senior citizens living alone were identified based on a nomogram. Moreover, the risk of depression in senior citizens living alone who had experienced suicidal ideation

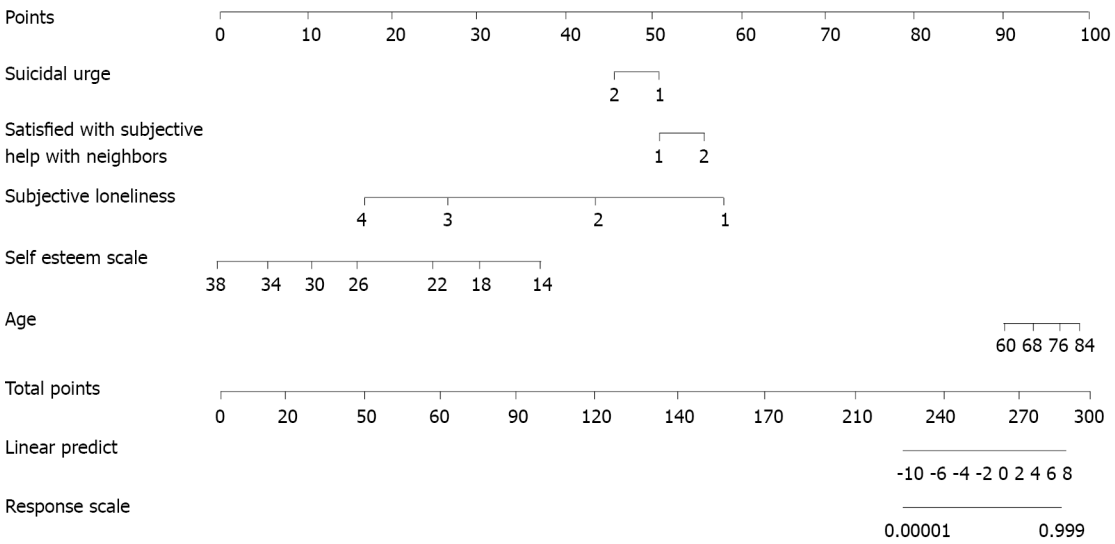


Figure 2 A nomogram for predicting the depression of elderly living alone.

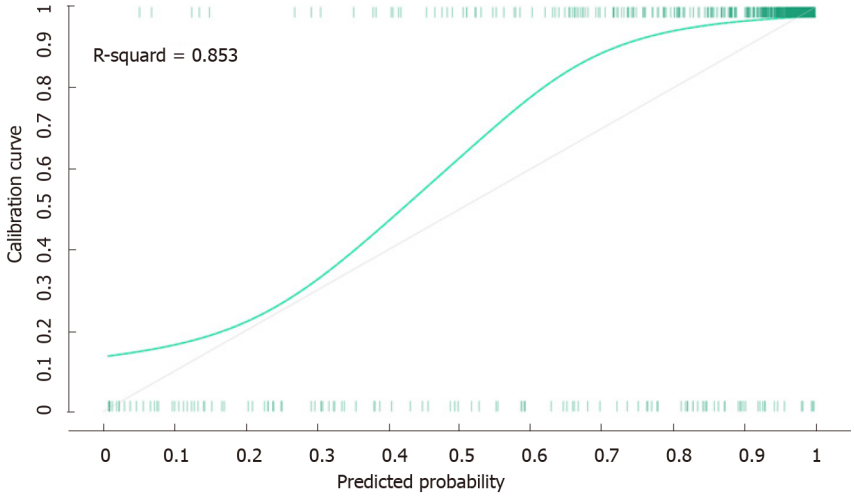


Figure 3 Calibration plot for nomogram model.

over the past year, were not satisfied with help (support) from neighbors, felt lonely, had low self-esteem (≤ 15 on the Rosenburg SES scale), and were ≥ 80 years old was 99.8%, which is very high. Therefore, screening this high-risk group for multiple risk factors and continuously monitoring them from a community perspective to prevent depression in the senile stage is urgently required.

Another finding of this study was that poor perceived social support or a weakened social network (social bonds and meaningful social contact[44]) was identified as a risk factor for depression in senior citizens living alone. A social network is a multidimensional concept that encompasses social relationships and factors such as the frequency of contact with family members, friends, and spouses; the degree of mutual assistance; and satisfaction with social relationships can be used to measure it[45]. Previously, several research groups have also reported that the lack of a social network is a major risk factor for depression in the elderly[41,43], which is in agreement with our results.

It has been reported that the reinforcement of a social network (such as support from acquaintances) can alleviate depression (*i.e.*, it is a preventative factor)[46]. In the case of senior citizens living alone, support from acquaintances such as neighbors can complement a lack of support from immediate family members and/or relatives. Senior citizens living alone and interacting with neighbors on equal terms is considered to be a very important element in their social networks. Park[47] reported that senior citizens who frequently met friends or neighbors had a significantly lower risk of depression and explained that this was because they received more social support when they met acquaintances more frequently. However, the results of the present

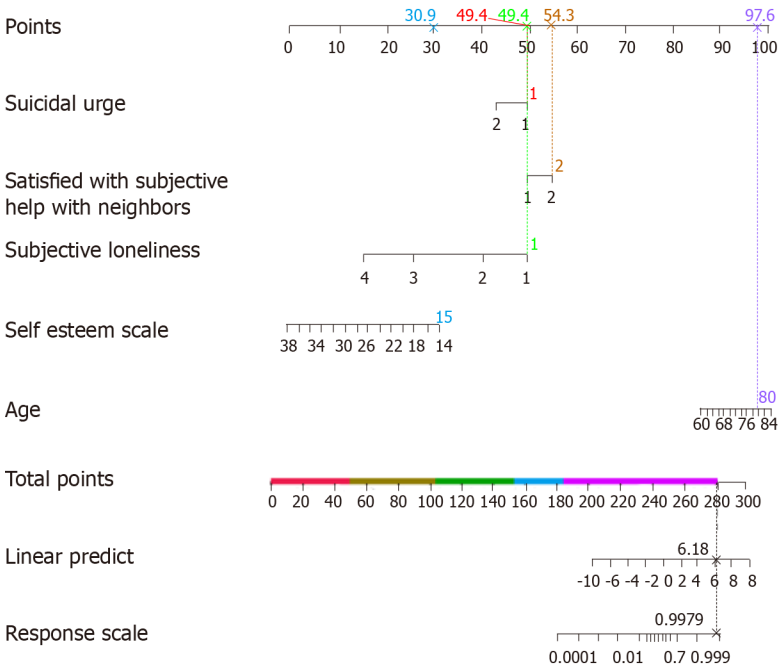


Figure 4 Application example of depression prediction nomogram for elderly living alone: Senior citizens who had suicidal urge over the past year, were not satisfied with subjective help with neighbors, thought that they were mostly lonely, had 15 points in the Self-Esteem Scale, and were 80 years or older.

study show that the frequency of contact with friends and neighbors (a quantitative factor) did not significantly affect the relationships in the social network whereas actual help (a qualitative factor) did significantly. Thus, this qualitative aspect of support that positively supported the emotional or economic problems of senior citizens living alone was more important than the number of meetings in the social network.

In summary, the results of the present study reveal that living alone due to the loss of a spouse and/or breakdown of the family network are more likely to cause emotional disorders such as depression. Moreover, strengthening qualitative aspects such as direct support from neighbors could more effectively lower the risk of depression than quantitative aspects such as the frequency of communication with family members or neighbors.

We identified factors related to depression in the elderly living alone using representative epidemiologic data and developed a nomogram that can help clinicians visually and conveniently identify the risk factors of depression, including social networks as well as demographic factors, which are the advantages of the study.

The limitations of this study are as follows: (1) We could not identify the severity of depression because we only analyzed the prevalence of depression in senior citizens living alone using a depression screening test, further studies are required to prove the risk factors of depression by identifying the severity of depression based on medical diagnosis; (2) We only used a self-report survey on the social isolation or social network of senior citizens living alone; a self-report survey poses the risk of recall bias, so in future studies, we will mitigate this by using interviews with social workers who regularly visit the homes of the senior citizens living alone and collecting data by using the Internet of Things; and (3) Since this is a cross-sectional study, it is impossible to determine causal relationships between the risk factors for depression in senior citizens living alone, and thus, a longitudinal study should be conducted in the future to achieve this.

CONCLUSION

The results of the present study imply that it is necessary to develop a support system customized for each senior citizen living along by strengthening his/her relationship network for preventing depression. Actual support from acquaintances such as neighbors (reinforcement of the qualitative aspect of the network) rather than the

frequency of physical contact (reinforcement of the quantitative aspect of the network) is key for protecting them from depression. Furthermore, establishing an improved mental health policy that identifies and continually manages groups of senior citizens living alone with a high risk of developing depression based on multiple risk factors is needed.

ARTICLE HIGHLIGHTS

Research background

Senile diseases are rapidly increasing globally due to the rapid aging of the population. Among these diseases, depression is an important and frequent psychia-tric disorder in the senile stage, and it is predicted to be the second major factor in the global burden of disease.

Research motivation

Although the number of senior citizens living alone is increasing, only a few studies have identified factors related to the depression characteristics of senior citizens living alone by using epidemiological survey data that can represent a population group.

Research objectives

This study developed a nomogram that allows physicians to check the multiple risk factors of depression of senior citizens living alone using visual graphs and to calculate the prevalence probability of depression while considering the personal characteristics of a subject based on these results.

Research methods

This study analyzed 1558 senior citizens (695 males and 863 females) who were 60 years or older. Depression, an outcome variable, was measured using the short form of the Korean version CES-D (short form of CES-D). This study built a depression prediction model using logistic regression analysis to find out the effect of each variable on depression. The developed depression prediction model contained a nomogram to make it possible for clinicians to interpret the prediction results easily.

Research results

In this study, the significant predictors of depression of the senior citizens living alone were the experiences of suicidal urge over the past year, dissatisfaction with help (support) from neighbors, subjective loneliness, age, and low self-esteem.

Research conclusions

The results of this study implied that it is necessary to develop a support system customized for subjects to strengthen the relation network for preventing depression in senior citizens living alone so that they can receive actual support from acquaintances such as neighbors rather than the frequency of physical contact.

Research perspectives

It is needed to establish an improved mental health policy that identifies high depression risk groups among senior citizens living alone based on multiple risk factors and continuously manages them.

ACKNOWLEDGEMENTS

The authors wish to thank the Korea Institute for Health and Social Affairs that provided the raw data for analysis.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1328-1345

DOI: 10.5498/wjp.v11.i12.1328

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Affect regulation in psychoanalytic treatments of patients with a borderline personality disorder–psychoanalysis and psychodynamic psychotherapy–a comparison

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Author contributions: Steinmair D engaged in writing and review of the original draft, editing and contributed to visualization and investigation; Wong G reviewed the final version of the manuscript (English language); Löffler-Stastka H engaged in the conceptualization and methodology, validation, provided resources, data curation, writing-original draft preparation, supervision, project administration; Frantal S was responsible for the software and performed the formal analysis; Rohm C contributed to the validation, KH, NF, MS, AHL, SM and GS investigation; all authors have read and agreed to the published version of the manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Medical University Vienna.

Informed consent statement: All

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Abstract

BACKGROUND

A recent meta-analysis has confirmed that the effects of psychotherapy on patients with borderline personality disorders (BPD) are still insufficiently understood. Evidence of differences between different types of therapies has been questioned.

AIM

To study repetitive interaction patterns in patients with BPD undergoing either psychoanalysis or psychodynamic therapy.

METHODS

Psychoanalysis (PSA) or psychodynamic psychotherapy (PDT) was administered to 10 patients each, the two groups were matched. Therapy regimens were applied according to care as usual/manualized including quality control and supervision as usual. Randomization to one of the groups was done after baseline assessment. During classical PSA (n = 10) and PDT (n = 10), semiannually, recordings (audio or video) of five consecutive therapy sessions were taken over three years for an ex-post analysis. The patients' characteristics, such as affect parameters [Affect regulation and experience Q-sort (AREQ)], quality of object

study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: Austria

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: February 23, 2021
Peer-review started: February 23, 2021
First decision: July 15, 2021
Revised: July 19, 2021
Accepted: November 20, 2021
Article in press: November 20, 2021
Published online: December 19, 2021

P-Reviewer: Koo BH
S-Editor: Fan JR
L-Editor: A

relations (quality of object relations scale) and personality traits [Shedler-Westen Assessment Procedure (SWAP-200)] were analyzed retrospectively by independent raters. Therapeutic action (psychotherapy process Q-sort) and affective (re)actions of the patients (AREQ) were then analyzed in relation to changes found in the patients' characteristics.

RESULTS

During the first year of therapy (PSA: n = 10; PDT: n = 9), the therapeutic method PSA was associated with significant improvements in the variable "SWAP Borderline", while in PDT change was not significantly different to baseline (PSA: P = 0.04; PDT: P = 0.33). Long-term results and follow up was available for seven participants in PSA and for five in PDT after three years; change in SWAP borderline for the whole sample was not significant at this time point when confronting to baseline (P = 0.545). However, differences between PSA and PDT were significant when analyzing the "mean change" in the SWAP Borderline variable after one year of therapy (P = 0.024): PSA led to slightly increased BPD symptoms, while PDT to a decrease; for the long run, variance of observed change was higher in PSA than in PDT (SD_{PSA} ± 9.29 *vs* SD_{PDT} ± 7.94). Our assumption that transference interpretations, closely followed by affective changes in the patient, could be useful modes of interaction was reproducible in our findings, especially when looking at the descriptive findings in the long-term data. The analysis of repetitive interaction structures demonstrated a very specific "time-lag" between therapeutic intervention and a corresponding increase in positive affect in successful therapy cases.

CONCLUSION

Exploring the change processes in the patients' characteristics and linking these changes to specific treatment strategies is of clinical importance when starting treatment and for its long-term progress.

Key Words: Psychoanalysis; Psychodynamic psychotherapy; Borderline personality disorder; Affect regulation; Affect regulation and experience Q-sort; Transference

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Core Tip: This is a retrospective study to evaluate similarities and differences between psychoanalysis (PSA) and psychodynamic psychotherapy (PDT) in patients with borderline personality disorder. Both treatments were adequately effective. However, interactional aspects varied between PSA and PDT, requiring further investigation and consideration in therapy.

Citation: Steinmair D, Wong G, Frantal S, Rohm C, Löffler-Stastka H. Affect regulation in psychoanalytic treatments of patients with a borderline personality disorder–psychoanalysis and psychodynamic psychotherapy–a comparison. *World J Psychiatr* 2021; 11(12): 1328-1345
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1328.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1328

INTRODUCTION

In treatment research and outcome studies, the specific factors within the therapeutic process which lead to clinically significant progress are often not as apparent as one might hope. This applies to classical psychoanalysis (PSA)[1] as well as to psychoanalytically oriented psychotherapy/psychodynamic psychotherapy (PDT)[2]. There is a lack of empirical data, particularly studies regarding psychoanalytic techniques, demonstrating the need for further research in this field[3]. Studies examining factors at work in the psychoanalytic process which determine outcome measures are rare[4, 5]. A major objective in psychoanalytic process research is the identification and validation of factors that lead to structural change and changes in maladaptive emotional patterns[6]. Intended for evaluating treatment progress, by examining

P-Editor: Fan JR

process factors in connection to outcome measures, the following variables were of importance for the present study.

Outcome measures–patient characteristics and influencing factors

One important point is that experiences that are affectively meaningful[7] and/or affects that are difficult to tolerate represent the essential catalysts for change. Several treatment studies have examined or even verified this hypothesis[8-10]. Affective instability and impulsivity due to impaired affect perception and regulation leading to intra- and interpersonal dysfunction are key features in patients with borderline personality disorder (BPD). Clinical researchers have suggested that attention be paid to affective experience, for it determines positive outcomes[11] (see also[12-14]). In this matter, one should attempt to specify which affective state in connection with a particular personality pathology (*e.g.*, quality of object relation[5]) should be dealt with, in order to achieve satisfying treatment outcomes. The next logical step would then be to identify to what extent therapeutic action during the analytic process is responsible for the observed therapeutic results[15].

Therapeutic action–active elements and mediators

Psychoanalytic treatment studies investigating therapeutic interventions, which are mainly based on psychoanalytic models of mental functioning[16], are quite rare. However, Jones and Ablon[17] and Jones[18] conceptualized the mode of therapeutic action, describing it as a "repetitive interaction structure"[17,18]. This empirically derived conceptualization, of the therapist-patient interaction, covers both therapeutic actions [*e.g.*, clarification, confrontation, (transference) interpretation] and the patient's (re)actions. Depending on the perspective, a patient's (re)action may be seen as a reflection of his/her own psychic structure, object representation, compromise formation or impulse-defence configuration. A similar concept is known as the "transference-countertransference-process"[4]. Kantrowitz[4] and Jones[18] were one of the first to claim that dynamic aspects in patient-therapist interactions, being resonant or dissonant, are essential to therapy results[4,18]. The "two-person-process" should therefore be explored, to widen our knowledge of patient characteristics, particularly of influencing factors (such as affect parameters, transference patterns, or object relations patterns), and most notably regarding the agents of therapeutic action. The role these influencing factors play in therapy outcomes is currently quite well researched (see the quality of object relations[5]). The mediating function of the quality of the therapeutic relationship between patient and therapist, which is configured early on in therapy (in general as early as in the 2nd session), has already been described by Blatt and Zuroff[19] (2005) as being extremely important for the therapeutic process[19].

Hence, questions arise of how therapeutic interaction styles during psychoanalytic treatments come about, how they are displayed and explored and how these modes of interaction can create a foundation for treatment progress and the change process in general. In the current study, affect parameters and character traits (item constellations), which have already shown predictive power for therapy outcomes in other samples[20], were compared to differentiate types of interaction styles. Our investigation was applied to PSA and PDT of BPD patients in a retrospective study: By analyzing recordings of sets of consecutive sessions of two matched groups of BPD patients. The hypothesis was that changes during the treatment process would only occur if specific therapist-patient interactions emerge. The therapist-patient interaction was hypothetically defined as being effective when therapeutic action was met, after a particular time interval, with an affective (re)action (meaning an increase in positive affects) in the patient.

Based on the hypothesis, that significant therapeutic interactions occur in both treatment forms, the objective of the study was to explore the differences between "classical psychoanalysis–PSA" and "psychodynamic psychotherapy–PDT". By employing therapy concomitant evaluations, first treatment outcomes and second interaction styles of the repetitive interaction structure were examined for differences.

MATERIALS AND METHODS

Therapeutic methods and therapists

Our study group took audio/videotapes of PSA sessions and PDT sessions semiannually. All participants and the therapists involved gave their informed consent.

PSA: Ten patients were treated at four sessions a week with PSA. Each patient was treated by a different therapist. The analysts had a minimum of five years of clinical experience in conducting psychoanalytic treatment and had completed their training at the Vienna Psychoanalytic Society [German: Wiener Psychoanalytische Vereinigung (WPV)/IPA]. Weekly supervisions, based on a modern, object-relational Kleinian model[21,22] and additionally two external supervisions, each performed every three months by two training analysts from the British Psychoanalytic Society (Segal H and Daniel P), verify the analytic quality of and therapy adherence to the therapeutic model.

PDT: Ten further patients were treated at two sessions a week with PDT. In this group also, each patient was treated by a different therapist. The therapists had completed their psychotherapeutic training according to the manual for PDT[14]. Supervisions, ensuring the quality of therapy and therapy adherence, were performed weekly by an experienced training analyst and PDT supervisor.

Psychoanalysis: In psychoanalytic treatment, non-directive listening is carried out with a neutral attitude, aiming to overcome sources of resistance, with the method of free association at the heart of the technique. Thus, although the analyst must get involved with the patient, he remains "equidistant" from the id, ego, and superego, as well as with respect to conflicts in the relationship and within the therapist himself [23]. Key psychoanalytic concepts (the unconscious, drives, defenses, object relations, Oedipus complex, transference) have a direct impact upon concepts for treatment technique (countertransference, interpretation, resistance)[24]. The analyst's focus is on the patient's mind during the therapy session rather than on the patient's existence in "external reality". The treatment goal is the development of ability for self-reflection and analysis, symbolizing and engaging in object relations.

Unlike in psychoanalytic oriented therapy, the higher frequency of the sessions provides a suitable framework for the analysis of hitherto abstract fears, wishes, and unconscious conflicts. However, as distinguished from PDT, the indication for PSA is sometimes limited due to lacking reflective functioning skills, ego-integration, and externalizing defense processes.

Therapists' adherence to the method taught by the Vienna Psychoanalytic Society (WPV/IPA) was ensured by supervision carried out on a regular basis, as described above.

PDT in patients with a borderline personality: For a more thorough description of the applied method, see the textbook of Burian and Grossmann-Garger[25]. Psychodynamic or "psychoanalytic-oriented" psychotherapy is derived from psychoanalysis, but it differs from it not only by the frequency of sessions, but also by the lack of the use of a couch[26]. The therapeutic activity is defined, rather, by a clear problem statement and by work on the alleviation of symptoms or on identity integration. This method emphasizes the importance of the patient's actual external reality, and emphasis is brought to the here and now[25]. Transference interpretation and analysis of the transference relationship aims for modification of internalized patterns regarding object relations, behavior, and affect perception and regulation. Treatment goals often imply work on a sense of consistency about who oneself and others are across time and different contexts[26].

In contrast with psychoanalysis, neutrality frequently has to be sacrificed because of danger arising from possibly destructive enactment, when patients seem unable to contain their inner psychic conflicts. Supportive interventions are sometimes necessary.

Adherence of the therapists to the manual[14] was ensured by the supervision carried out at a regular basis mentioned above.

Participant population

We applied a hot spot recruiting strategy that allowed for a matched pair design. The patient recruitment timeframe was four years. All patients willing to participate in the study, and fulfilling the inclusion criteria were included in the study. Participants treated with PSA and PDT were matched according to age, gender, DSM-IV-TR diagnosis[27] (Diagnostic and Statistical Manual of Mental Disorders, DSM, American Psychiatric Association 2000), pathological personality traits, assessed using Shedler-Westen Assessment Procedure-200 (SWAP-200)[28], and Kernberg[29]'s structural diagnosis. The audio/videotape analysis of recorded sessions and comparing the two therapeutic methods applied was carried out only after the completion of three years of psychotherapy. Thus the analysis's findings did not influence the therapeutic interventions. All patients showed the structural diagnosis of a BPD[29]. All

participants underwent Structured Clinical Interview for the DSM-IV-TR Disorders and an examination by a psychiatrist (*i.e.*, care and quality control as usual). Only participants fulfilling the DSM-IV diagnosis of BPD were included in the study. The participants had the following DSM-IV diagnosis of axis 1 comorbidities: Major depression, dysthymia, depression, anxiety disorder, eating disorder (22%: 296.00, 17%: 300.4, 10%: 311, 39%: 300.0, 12%: 307.0). The study included 20 patients, with an average age of 31 years (± 9). Patients were randomly assigned to therapists, often depending on the availability of a therapist.

The sample consisted of four (20%) male and 16 (80%) female patients with a relatively high level of education: While three patients (15%) only finished compulsory school, 14 patients (70%) were high school graduates and three (15%) had a university degree. Most of the patients (17) were single (85%); however, two (10%) were married, and one (5%) was divorced. One patient from the PDT group was excluded from the analysis since only baseline data were collected for the patient, and no further data on therapy development during the follow-ups were available. In Table 1, further descriptive analysis of the patient population, including mean SWAP profile scores, for both therapy groups (PSA *vs* PDT) is presented.

Ethic: Approval from the ethics committee of the City of Vienna and the Medical University of Vienna was given; EK Nr.: 2169/2013. This study was done in accordance with the terms set forth in the Declaration of Helsinki. Written informed consent was given.

Design

After obtaining informed consent for this observational study, treatment sessions of twenty patients were recorded semiannually over a period of three years. In the case of PSA, treatment sessions were assessed using verbatim transcripts and audio recordings of the peer-supervisions as well as external supervisions, while in the case of PDT, sessions were assessed using video recordings.

From the beginning of therapy, in an interval of six months, recordings (audio or video) of five consecutive therapy sessions were analyzed for patient characteristics and interactions, using the following instruments.

Instruments analyzing patient characteristics

SWAP-200: Character traits were determined using the SWAP-200[24,26], assessed by two independent external raters, both of whom were medical students, each having at least six years of experience with the instrument; with adequate training, they regularly underwent assessments of inter-rater reliability. Their inter-rater reliability showed a constant κ_{mean} = 0.69. The SWAP-200 is a personality assessment instrument for use by clinically experienced mental health professionals requiring a professional assessment (*e.g.*, during an ongoing therapeutic engagement) or a systematic clinical research interview. Test-retest reliability for the instrument is r = 0.85 for the SWAP's trait and personality disorder dimensions. The mean reliability when comparing to DSM-IV personality disorders was 0.90 for SWAP scales. Multiple research groups in multiple samples have provided strong evidence, qualifying SWAP-200 as a reliable and valid measure independent from applied methods[30]. The SWAP is based on the Q-sort method, and thus it uses a fixed score distribution, with items being rated as more or less descriptive of a person, with the possibility of detecting even fine nuances.

Based on the SWAP-200 scoring systems, personality score profiles are generated. The scores are standardized scores (T-scores) based on norms established in a clinical sample[28]. Scores indicate the match between a patient and a diagnostic prototype derived either from DSM-IV diagnostic categories (which include the personality disorders in DSM-IV as well as depressive personality disorder) and/or an alternative set of personality syndromes derived empirically (*via* Q-factor analysis, see SWAP manual). Thus, a high degree of overlap with the SWAP-profile "dysregulated/borderline" *(i.e.*, variable SWAP-borderline") indicates that the degree of resemblance between the actual patients with the diagnostic prototype representing the personality disorder is also very high. The "Borderline/Emotionally Dysregulated" personality is described as overlapping with the DSM-IV construct. Patients with this profile lack affect-regulation (intense and volatile affect) and show states of desperation and despair with a tendency to self-harm[31].

Affect experience and affect regulation Q-sort (AREQ): Affective experience and affect regulation were assessed using the affect regulation and experience Q-sort AREQ[32,33]. The AREQ is an expert-rating, 98-item Q-sort test, exploring affective functioning using an interview. Sufficient convergent and discriminant validity have

Table 1 Descriptive analysis of the patients in the therapy groups psychoanalysis and psychodynamic psychotherapy

	PSA (*n* = 10)	PDT (*n* = 9)	*P* value[1]
Mean age (yr)	30.4 ± 7.5	31.9 ± 10.2	0.719
Sex	8 f, 2 m	7 f, 2 m	0.912
Therapeutic dose (mean)	390 sessions	124 sessions	0.001
DSM IV axis II diagnosis	Borderline personality disorder		
Structural diagnosis	Borderline personality organization		
SWAP diagnosis			
Paranoid	49.37	48.85	0.871
Schizoid	49.65	54.79	0.201
Schizotypal	51.27	53.72	0.475
Antisocial	49.22	45.62	0.132
Borderline	52.97	48.62	0.289
Histrionic	53.92	46.37	0.127
Narcissistic	50.86	46.56	0.249
Avoidant	47.78	54.18	0.037
Dependent	49.29	52.01	0.233
Obsessive-compulsive	47.65	52.51	0.245

[1]*P* value calculated using ANOVA. PSA: Psychoanalysis; PDT: Psychodynamic psychotherapy (*i.e.*, psychoanalytically oriented psychotherapy); SWAP: Shedler-Westen Assessment Procedure.

been shown. Affect experience includes the following three factors: Socialized negative affect, positive and intense negative affect, and affect experience, the latter of which itself includes reality focused response, externalizing defense, and avoidant defense [32]. The inter-rater reliability of two independent raters, both having an average of six years of experience with the instrument, showed an average $\kappa = 0.70$. They were both medical students, undergoing regular training and quality assessment.

Quality of object relations scale (QORS): The quality of object relations was evaluated by two independent external raters, using the QORS[33,34], and showed an inter-rater reliability of $\kappa_{mean} = 0.69$. The raters were both medical students, undergoing regular training and quality assessment. The QORS is an interview-based expert-measure with adequate criterion-related, construct validity[35]. The QORS assesses personality pathology with respect to object-relational maturity. Object relations are intrapsychic representations of self- and objects which arise out of emotionally important early relationships. The level of object relations is a known factor related to the outcome of psychotherapy. The interview scale consists of five levels of object-relational patterns with the manual giving explicit criteria for each of them and a description of prototypical cases. The rater distributes a total of 100 points, allocating them to five object-relational levels: Primitive, searching, triangular, controlling, and mature (for a thorough description of the method see[35]). According to Lindfors and colleagues, low quality of object relations is characterized by discontinuity and devaluation in relationships, with poor self-confidence and major separations in childhood identified as predictors of low-QOR[35].

Instruments analyzing processes occurring during therapy

Psychotherapy relationship questionnaire (PRQ): The quality of the psychotherapeutic relationship was assessed using the German version[36] of the PRQ[37]. With the help of 90 items, five dimensions of transference relationship patterns (hostile, narcissistic, anxious/preoccupied, avoidant/counter dependent, and sexualized) as well as a positive working alliance (secure/engaged) can be differentiated. The dimension "positive working alliance" is of particular interest to the current study, and as Bradley *et al*[37] and Tanzilli *et al*[38] have already shown, it acts as an indicator for the quality of the working relationship between patient and therapist, which in turn, strongly predicts treatment outcome in psychotherapy[39].

Psychotherapy process Q-sort (PQS): Patient-therapist interrelation variables were assessed using the PQS[40,41]. For this study, in order to analyze the process occurring during therapy, only items related to therapeutic action were utilized[41] (Table 2). From a psychoanalytic perspective, these items specifically covered transference interpretations considering the "total situation" described by Joseph/Astor[42]. The goal was to evaluate dyad-specific interaction structures, which are recurrent, mutually influencing patterns of interrelation between therapist and patient, whose experience, recognition, and understanding are fundamental elements of therapeutic action[17,34]. Therapeutic action was evaluated by two independent raters (κ_{mean} = 0.84) using the items presented in Table 2.

The raters were medical students, undergoing regular training, interrater assessments, and quality control.

Statistics

The statistical methods of this study were performed and reviewed by a biomedical statistician, Sophie Frantal, from the Medical University of Vienna before submission.

To begin with, a descriptive analysis (mean, standard deviation, minimum and maximum) of the variables of interest was created. However, due to the rather small sample-size, also ranges were used to characterize the sample. Next, the differences between the two groups (PSA and PDT), based on pre-post comparison of the main factor "SWAP Borderline"[28], were examined. For this purpose, the scores at the beginning of therapy (*t1*), after one year of therapy (*t3*) and after three years of therapy (*t7*), were evaluated. Also, additional factors possibly influencing outcome, such as age, gender, education, family status and gender of the therapist, were included in the analysis. Missing values, detected after data documentation, were excluded from the analysis. To answer the question dealing with the differences between the two therapeutic methods in concern to the changes observed in the variable "SWAP Borderline", all variables of interest were tested in univariate analysis (linear regression or variance analyses). Only variables that showed statistically significant p-values in the univariate analysis were subsequently tested in a multivariate linear model (ANOVA or ANCOVA). Furthermore, effect size was also calculated for groups PSA and PDT.

In the following step, differences between the two therapy groups concerning the factors "positive affect" (AREQ), "QORS-total score", "therapeutic action" (PQS), and "positive working alliance" (PRQ) were assessed. These factors were explored in the same manner as the factor "SWAP Borderline". Similarly, in the cases, where the variable of interest "therapeutic method" did not show any statistically significant effects, no further risk factors were analyzed. The number of therapy sessions ("therapeutic dose"), defined as the mean number of sessions in which each therapeutic method (PSA *vs* PDT) was applied, was also tested as a factor possibly having influence on the variable "Borderline".

Analyses were performed using the "freeware" program R.2.8.0[43] and SPSS Statistics version 17.0. $P < 0.05$ were considered to be statistically significant.

RESULTS

Progress results

The differences between the two therapeutic methods, PSA and PDT, with regards to the main variable "SWAP Borderline", are presented in Table 3. Even though the differences are not significant, a simple comparison between the mean values shows that borderline pathology, in the case of PSA, continuously decreases. However, in the PDT group, it primarily increases, particularly in the first year. This observation is also reflected in the effect size: d = 0.79 after one year of PSA, d = 0.88 after three years of PSA, d = 0.04 between first and third year of PSA; d = |0.40| after one year of PDT, d = 0.04 after three years of PDT, d = 0.33 between first and third year of PDT. After three years of PDT, the main variable "Borderline" improves considerably compared to the values measured after the first year of PDT, whereupon the therapeutic method PSA shows less change in the same time span. This, however, must be interpreted with caution, due to the fewer number of patients after three years of therapy (three dropouts in PSA, four dropouts in PDT after three years). Even tough, the dropout rate is not surprising, as it might be related to the frequent alliance ruptures typical for borderline pathology, and the naturalistic design must be considered before generalizing this finding. However, looking beyond the main variable and more at individual items in detail, in both groups, patients who dropped out were charac-

Table 2 Items from the psychotherapy process Q-sort–that were applied to assess therapeutic action in the present study

Item	Description
2	Therapist draws attention to patient's non-verbal behavior, *e.g.*, body posture, gestures
22	Therapist focuses on patient's feelings of guilt
28	Therapist accurately perceives the therapeutic process
36	Therapist points out patient's use of defensive maneuvers, *e.g.*, undoing, denial
40	Therapist makes interpretations referring to actual people in the patient's life
50	Therapist draws attention to feelings regarded by the patient as unacceptable (*e.g.*, anger, envy, excitement)
62	Therapist identifies a recurrent theme in the patient's experience or conduct
65	Therapist clarifies, restates, or rephrases patient's communication
67	Therapist interprets warded-off or unconscious wishes, feelings, or ideas
79	Therapist comments on changes in patient's mood or affect
80	Therapist presents an experience or event in a different perspective
82	The patient's behavior during the hour is reformulated by the therapist in a way not explicitly recognized previously
93	Therapist is neutral
98	The therapy relationship is a focus of discussion
100	Therapist draws connections between the therapeutic relationship and other relationships

Table 3 Differences in the variable "Shedler-Westen Assessment Procedure Borderline" measured at baseline (*t1*), after 1 yr of therapy (*t3*) and after 3 yr of therapy (*t7*) (mean ± SD)

		n (%)			Min	Max	*P* value[1]	*dt3*[2]	*dt7*[2]
Baseline (*t1*)	PSA	10	52.97	8.73	42.69	71.88		0.79	0.88
	PDT	9	48.62	8.56	40.23	67.63		|0.40|	0.04
	Total	19	50.90	8.70	40.23	71.88	0.289	0.24	0.45
After 1 yr of therapy (*t3*)	PSA	10	46.26	8.21	29.99	60.21			0.04
	PDT	9	51.80	7.49	40.26	65.30			0.33
	Total	19	48.88	8.17	29.99	65.30	0.145		0.20
After 3 yr of therapy (*t7*)	PSA	7	45.96	6.75	37.63	56.78			
	PDT	5	49.01	10.20	38.90	61.33			
	Total	12	47.23	8.07	37.63	61.33	0.545		

[1]*P* value calculated using ANOVA.
[2]*d* = Cohen's. *d*: Represents effect size measured after 1 yr (*t3*) and after 3 yr (*t7*) of therapy.
PSA: Psychoanalysis; PDT: Psychodynamic psychotherapy; SWAP: Shedler-Westen Assessment Procedure; SWAP-borderline: SWAP personality syndrome "dysregulated/borderline".

terized by an increase of projective mechanisms (projection, projective identification) as displayed in SWAP-Item 076 and Item 116. This was observed mainly during the first year (Figure 1), but generally persisted until the moment a patient dropped out of therapy. Additionally, it was observed that these patients and their therapists showed low scores in the PQS-Item 36, 50 (displaying therapists' work on defensive mechanisms) and PQS-Item 28 (therapists' accurate perception of the therapy process) (Table 2). These ratings might display a lack of ability to perceive, contain and work through the projective mechanisms in the therapeutic relationship (Figure 1), which was also observed and discussed in the supervision group. Interestingly, drop-out patients' pressure and usage of projective mechanisms were low at the beginning of both forms of therapy compared to continuing and finishing patients, who presented higher amounts of projective identification at the beginning of therapy. Also, PQS Items 36, 50, and 28 (Table 2) were higher in cases where therapy reached completion.

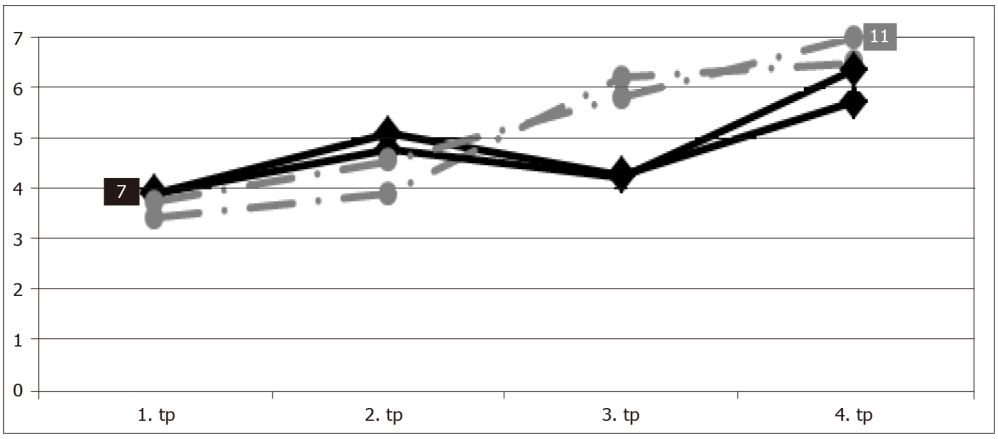


Figure 1 Course of Shedler-Westen Assessment Procedure-items 76 and 116. Course of sensible Shedler-Westen Assessment Procedure-Items 076 ('7', black) and 116 ('11', grey) both assessing "projective identification" (Item 076: "Manages to elicit in others feelings similar to those he or she is experiencing" (*e.g.*, when angry, acts in such a way as to provoke anger in others; when anxious, acts in such a way as to induce anxiety in others); Item 116: "Tends to see own unacceptable feelings or impulses in other people instead of in him/herself."). Disrupted line: Broken off treatment, continuous line: Completed treatment; *tp*: Half-yearly measurements showed a significant effect of time ($P = 0.004$). SWAP: Shedler-Westen Assessment Procedure.

As far as the drop-out patients could be reached, they reported no increase in self-harming behavior; one was referred to supportive therapy by the therapist due to the development of psychotic transference.

First year of therapy–outcome variables

Considering the patients' characteristics, changes in borderline pathology and, simultaneously, improvements in the quality of object relations were observed, when both forms of therapy were taken into account. With regard to the patient, an increase in the ability to recognize positive affects was observed during PSA, while a decrease in the same category was seen during PDT. However, an increase in therapeutic action was observed during PDT, while therapeutic action during PSA treatment stayed constant. Concerning the working alliance, a reduction in the positive working relationship between therapist and patient was noted during PSA treatment, whereas an increase in the same category was observed during PDT. The descriptive analysis of the pre-post variables (SWAP-Borderline, AREQ-positive affect, QORS-total score, PRQ-positive working alliance and PQS-therapeutic action), defined as the difference between the values of each variable at beginning of therapy (*t1*) and after one year of therapy (*t3*,) is presented in Table 4 ("SWAP-borderline" = SWAP personality syndrome "dysregulated/borderline"). All means were close to zero (with the exception of "SWAP-Borderline"), showing little to no difference between baseline and follow up (after one year) measurements (Table 4: "mean"). Only the variable "SWAP-Borderline" showed a negative response during the first year of PDT treatment (*i.e.*, less BPD symptoms), and a positive value in the PSA treatment (*i.e.*, more BPD symptoms) however, the standard deviation was in this case somewhat higher than in the other variables (mean SWAP Borderline PSA = 6.71; SD ± 9.29; mean SWAP Borderline PDT = -3.18; SD ± 7.94).

In univariate analysis, the difference between the two therapeutic methods in concern to changes in the variable "SWAP Borderline" was examined and was shown to be significantly different (PDT: Estimate 4.07; T = 2.19; SD ± 1.73; $P = 0.402$; Table 5). The age of the patients was found to not be significantly different, with a $P = 0.087$, however it still displayed a strong trend, with younger patients showing better results (Table 5). Thus, it is evident that during the first year of therapy, the therapeutic method PSA led to a higher decrease regarding the symptom profiles reproduced in the variable "SWAP Borderline" than the therapeutic approach PDT (Table 3). Nevertheless, a higher variance of individual therapy results after the first year occurred in PSA (Table 3). Thus, when looking at the mean change in the variable "SWAP Borderline" after one year, PDT showed a significantly more pronounced improvement (Table 4). Sex, education, and family status of the patient as well as the sex of the therapist were not found to be significant. A multivariate analysis, regarding the risk factors therapeutic method and patient age, was also performed and the following results were found: In both cases, the levels of significance did not change and the therapeutic method remained significant (PDT: Estimate 4.01; T = 2.33 ± 1.73; *P*

Table 4 Changes in patient characteristics, borderline pathology, and object relations after one year of therapy (mean ± SD)

				Min	Max	*P* value
SWAP Borderline	PSA	6.71	9.29	-1.58	29.58	0.024[a]
	PDT	-3.18	7.94	-10.61	15.22	
	Total	2.02	9.85	-10.61	29.58	
AREQ positive affect	PSA	-0.11	0.98	-1.57	1.86	0.513
	PDT	0.19	0.86	-0.94	1.43	
	Total	0.03	0.91	-1.57	1.86	
QORS total score	PSA	-0.20	0.73	-1.60	0.90	0.726
	PDT	-0.34	0.75	-1.70	0.50	
	Total	-0.26	0.72	-1.70	0.90	
PRQ positive working alliance	PSA	0.15	0.35	-0.33	0.50	0.339
	PDT	-0.27	0.73	-1.08	0.50	
	Total	-0.08	0.60	-1.08	0.50	
PQS therapeutic action	PSA	-0.00	0.60	-0.73	1.00	0.318
	PDT	-0.28	0.45	-1.07	0.47	
	Total	-0.14	0.53	-1.07	1.00	

[a]*P* < 0.05. Mean differences ("mean") regarding the mean scores of the relevant variables ("Shedler-Westen Assessment Procedure-borderline", "Affect experience and affect regulation Q-sort-positive affect", "Quality of object relations scale total score", "Psychotherapy relationship questionnaire-positive working alliance", "Psychotherapy process Q-sort therapeutic action") between the score at baseline *vs* the score after the first year of therapy (t1 minus t3, where t1 represents measurements taken at baseline and t3 after 1 yr of therapy). PSA: Psychoanalysis; PDT: Psychodynamic psychotherapy; SWAP: Shedler-Westen Assessment Procedure; AREQ: Affect experience and affect regulation Q-sort; QORS: Quality of object relations scale; PRQ: Psychotherapy relationship questionnaire; PQS: Psychotherapy process Q-sort.

Table 5 Univariate analysis of the variable "Shedler-Westen Assessment Procedure Borderline" (mean ± SD)

Patient characteristics	Estimate		T value	*P* value
PDT group	4.07	1.86	2.19	0.042[a]
Sex of patient	2.89	5.18	0.56	0.584
Sex of therapist	7.15	4.24	1.68	0.109
Education: Apprenticeship	12.21	10.49	1.16	0.261
Education: Vocational school	3.15	8.29	0.38	0.709
Education: High school	-2.80	5.78	-0.48	0.635
Married	-1.03	7.19	-0.14	0.888
Divorced	-0.39	9.90	-0.04	0.969
Age	0.41	0.22	1.81	0.087

[a]*P* < 0.05. SWAP-borderline: Shedler-Westen Assessment Procedure personality syndrome "dysregulated/borderline"; PDT: Psychodynamic psychotheray.

= 0.033), while patient age continued to not reach the fixed significance level (Age: Estimate 0.40; T = 1.98 ± 0.20; *P* = 0.064).

Secondary variables

Examining the four secondary variables during the first year of therapy, no statistically significant differences could be found between the two types of therapeutic methods (PSA *vs* PDT): AREQ-positive affect (estimate -0.31; T = -1.70 ± 0.18; *P* = 0.117), QORS-total score (estimate 0.08; T = 0.38 ± 0.20; *P* = 0.714), PRQ-positive working alliance (estimate 0.00; T = 0.01 ± 0.26; *P*= 0.993) and PQS-therapeutic action (estimate 0.14; T = 1.01 ± 0.14; *P* = 0.333). Consequently, no further calculations and analyses were

performed, regarding the secondary variables. Similarly, no significant changes were found in the variable "therapeutic dosage" (P = 0.298). However, the changes observed after time-point *t5*, *i.e.*, after 2.5 years of PDT, resulting in a constant decrease in borderline pathology, is quite interesting (difference in "SWAP Borderline", in the 175th session mean was -9.08; in the 245th session mean was 15.22). In the therapeutic method PSA, a constant decrease in borderline pathology is seen from the start.

"Repetitive interaction structures," which are defined as responses of the patient towards therapeutic action with an increase in positive effects, are depicted in Figure 2. The graph illustrates a sequence of five consecutive sessions measured on a semi-annual basis. However, it is essential to mention that Figure 2 is merely a graphic presentation of the data since therapeutic action had no significant influence on the variable "SWAP Borderline". The main finding is depicted in Figure 2: The time-lag of the repetitive "interaction structures" in PSA is shorter (approximately two/three sessions) than the time-lag observed during PDT (about five sessions). Thus, the descriptive analysis showed patterns quite distinct for each method.

Qualitative analysis of interactive patterns, example

With respect to PSA, a qualitative analysis of character traits with the SWAP showed repetitive patterns of trait fluctuations over the course of three years. The interpretation of the object-relationship dyad in transference with patient-, therapist-, and interaction-variables carried out with the PQS showed repetitive patterns of interaction when treatment was successful. PQS patient items and interaction items showed a rise in patient items when "interaction structure" items were rated as low and vice versa (Figure 3). In unsuccessful therapy attempts, in neither the SWAP nor in the PQS/AREQ ratings did similar patterns manifest, with a relatively constant course over time (not shown). When looking at a set of five consecutive sessions, positive affective response (measured with the AREQ) increased following therapeutic interventions, with a time-lag phenomenon manifestly present (Figure 4). Qualitative analysis revealed shorter time-lag for the positive affective response of the patient towards the therapists' interaction in PSA in contrast to PDT (Figure 2; PSA two/three sessions, PDT five sessions).

DISCUSSION

The combined analyses of repetitive patient-therapist interaction structures (AREQ, PQS) and patient characteristics (SWAP-200, AREQ, QORS) performed in this study have met the demands for therapy concomitant evaluations, which were briefly mentioned in the introduction and have also been described in the literature[10]. By means of such therapy concomitant evaluations, where the assessment of therapeutic techniques and changes in patient characteristics are combined, the possibility of specifying specific therapeutic methods is opened up.

Changes in patient characteristics

Our results have shown that patients, who were treated with PDT in the same time frame as patients treated with psychoanalysis proper, showed similar changes in the quality of object relations and affect parameters, albeit, however, with considerably distinct changes in personality pathology.

The increase in borderline pathology at the beginning of the PSA treatment is quite noticeable (mean change in SWAP borderline: PSA +6.71, PDT -3.18) with a higher variance of observed changes in the PSA group especially in the first year of therapy (Table 4). However, after one and after three years of therapy, mean “SWAP borderline” score was lower in the PSA group, while in the PDT group this score was even slightly increased.

These results indicate that indications for the two different methods must be assigned wisely, as they are not interchangeable.

Although all patients were diagnosed with BPD at the beginning of treatment, the two groups differed in the first six months of therapy. Considerably more patients in the PDT group were affected by social inhibitions (avoidant/self-conscious traits) and discomfort in social (schizoid traits) and close relationships (schizotypal traits). Borderline patients with schizoid personality pathology, treated with PDT, showed improvements, especially after the first year of therapy, while corresponding patients in the parallel group, treated with PSA, showed positive changes right from the start. Similar results have been reported in the Anna Freud Center study[44], where the psychoanalytic treatment of young patients with borderline and narcissistic

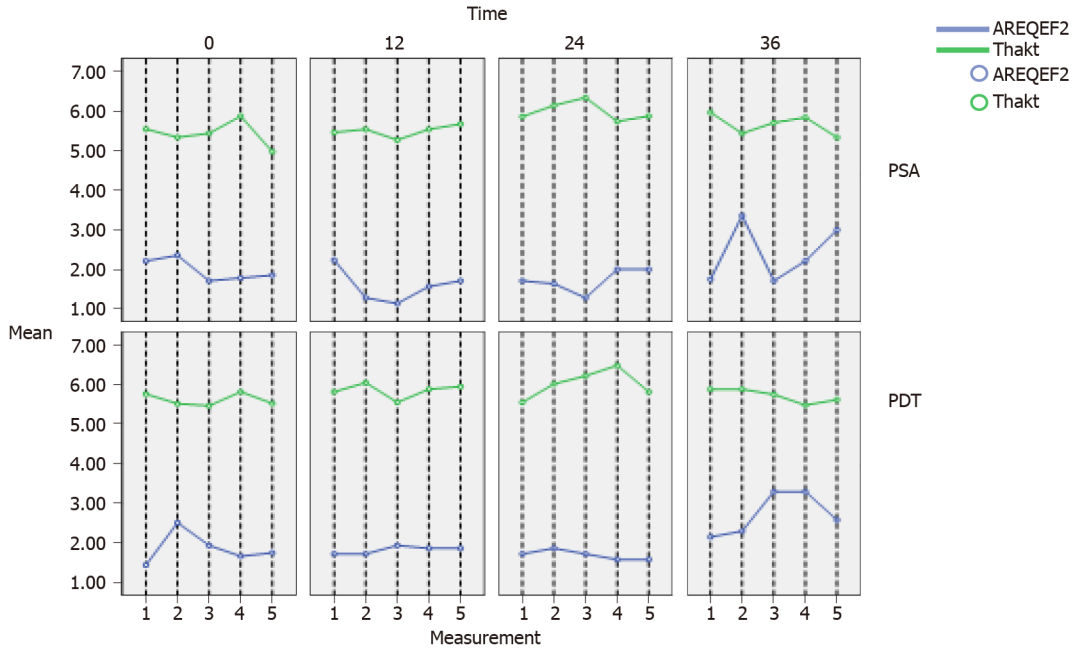


Figure 2 Therapeutic action and positive affect. The evaluation of therapeutic action ('thakt', *i.e.*, psychotherapy process Q-sort-therapeutic action) and positive affects in patients ['Affect experience and affect regulation Q-sort (AREQ)-EF2', *i.e.*, AREQ-positive affect] was performed semi-annually in five consecutive therapy sessions (measurement 1-5). The results of the annual measurements (baseline, 12, 24 and 36 mo) of thakt and AREQ-EF2 (mean) are presented in the figure for the psychoanalysis and for the psychodynamic therapy group. PSA: Psychoanalysis; PDT: Psychodynamic psychotherapy.

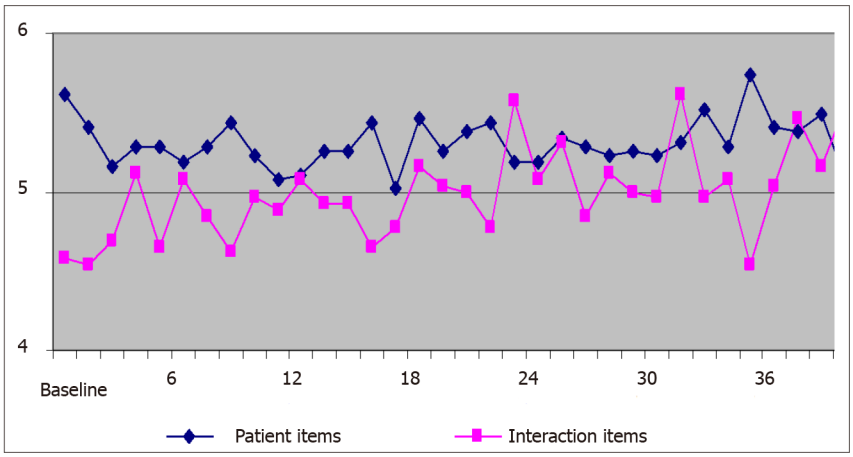


Figure 3 Patient-therapist interactions. Object-relation dyad measured with psychotherapy process Q-sort. Patient items are shown in blue, "interaction structure items" are shown in magenta. The follow-up was > 36 mo.

personality disorders was performed at different frequencies (five times *vs* once *per* week) and then ultimately compared. The problems encountered with narcissistic personalities of not being able to accept interpretations[45] or creating transference configurations, where the analyst becomes a shut-out observer[46], are more likely to be solved during PSA.

In the descriptive analysis of the secondary moderating and mediating variables, it appeared that in higher-frequency therapeutic methods, such as PDT, therapeutic action increased during the first year of therapy. This observation could possibly be related to the therapists' more vigorous focus on the working alliance (see an increase in a positive working relationship). But, one can only speculate here, since the secondary variables did not show any statistically significant differences between the two therapeutic methods. The therapeutic dose, interestingly, also did not show any statistical significance, by which closer observation of the interaction process becomes more relevant.

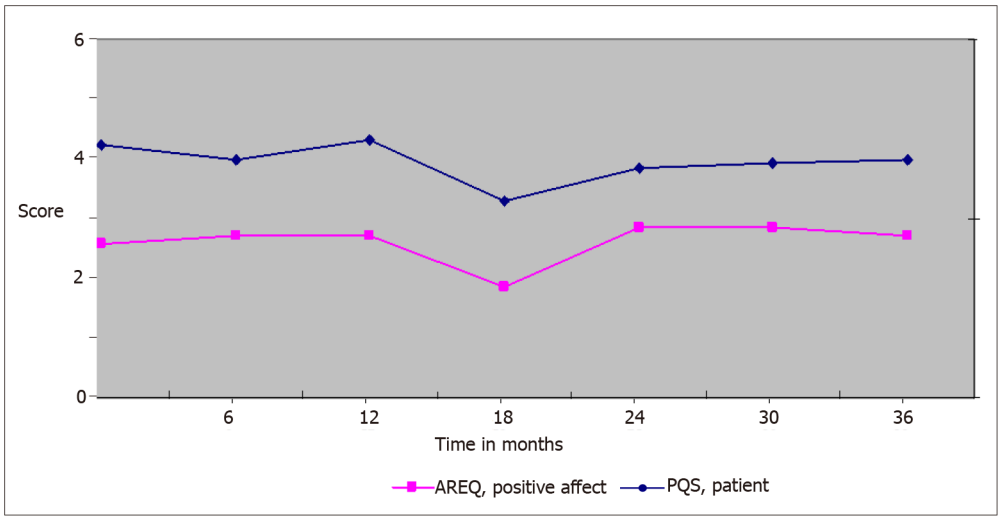


Figure 4 Affective response and psychotherapy process: Case example. Affective response (Affect experience and affect regulation Q-sort: Positive affect, shown in magenta) and therapeutic interaction structures (Psychotherapy process Q-sort: Shown in blue) over the course of 36 mo. PQS: Psychotherapy process Q-sort; AREQ: Affect experience and affect regulation Q-sort.

Interaction process

Psychoanalyses, with quick interactions (meaning that a therapeutic action is followed by an increase in positive affects in the patient within the next two to three sessions, *i.e.*, within two or three days), show a continuous decrease in the borderline pathology. Transference interpretations[42,47], closely followed by affective changes in the patient, present the most effective interaction styles in PSA. Strachey[48] described, taking into consideration Melanie Klein's theory, the role of projection and introjection in the analytic situation: The patient projects impulses and aspects of his/her inner world onto the analyst and then reacts upon these (projected aspects) as if these elements were part of the analyst[21,48]. Strachey[48] stressed, that changes in one's psyche are possible, when the previously described phenomena are analyzed step by step (*e.g.*, by analyst-centered interpretations), as it is often done in psychoanalysis[47-49]. Interactional micro-processes occurring during psychotherapeutic treatment (*i.e.*, body language, facial expressions and facial micro expressions, expression in words and ideas) provide cues about unconscious fears, wishes and conflicts. These enactments lead to a countertransference reaction in the therapist often outside of awareness at first. By getting to know patients' affect perception, processing, and expressions, therapists can provide interpretations and analysis.

Clarification and confrontation, as well as the interpretation and working through of the external reality of the patient, play a large role in higher-frequency therapeutic methods such as PDT[50]. Patterns in social interaction and ways of problem-solving are enacted in the patient-therapist setting, a thorough observation of such enactments (manifesting in language, gesture, facial expression, and micro-expression) is crucial for the detection of unconscious and preconscious material. This interactivity in the learning environment provided by the therapeutic setting leads to improved problem-solving and achievement of new perspectives.

The interaction styles in the PDT group of our study were slower; therapeutic actions and respective positive affective reactions of the patients were often observed to extend over three or four sessions (*i.e.*, two weeks). This difference, observed in the descriptive analysis, could possibly be due to different session frequencies, setting, or therapeutic techniques. Meltzer[12] and Etechegoyen[51] have pointed out, that at the beginning of treatment mostly externalizing, projective mechanisms can be observed [12,51]. If these projective mechanisms are not understood and treated promptly and sufficiently, unsatisfactory therapy outcomes will be then more likely. The worsening of the borderline pathology could hypothetically be associated with the therapists' focus mainly on external reality and working alliance, without employing transference (optionally analyst-centered) interpretations.

Limitation

While assigning patients to the two therapy groups, PSA and PDT, despite the known heterogeneity of BPD patients[52], we attempted to match patients who were comparable to one another, as far as their personality structure was concerned;

however, differences in the patients' personality traits were found in both therapy groups. The fact that the assigning of patients to therapy groups depended on the availability of a therapist may be seen as a legitimate point of criticism. These differences, however, were only found to be significant in patients with avoidant traits and may therefore be seen as having an only minor influence on the total outcome. As for the "therapeutic dosage", it would be of further scientific interest, to systematically research the relationship between the number of treatment sessions and therapy outcome. This study showed no significant differences in this matter.

Treatment of patients with the borderline disorder has traditionally been limited due to high drop- out rates already within the first months of treatment in outpatient settings (by the six-month point only 34% to 57% of BPD outpatients remain in treatment[53,54]). Although BPD has a known positive trajectory over time, comorbidities[55] are frequent and long-term functional recovery is difficult, with short-term therapies often not addressing the underlying problematic personality traits[56]. Thus, in our clinical understanding, the analysis of the characteristics of early patient-therapist interactions is essential due to known difficulties in collaboration with BPD[53,54]. One strength of this study is that complete long-term follow-up data (three years) were available for a majority of the participants (*i.e.*, PSA: 70%, PDT: 50%). Future research should investigate the specific drop-out process in BPD and further investigate factors that may improve long-term outcome, like repairing alliance ruptures.

Our research was carried out in a naturalistic manner, conducting on-site assessments. Thus, the observed phenomena resemble the 'real world'. Hypothesis-generating clinical research does not replace hypothesis-testing, but it can facilitate the development of a specific hypothesis that can be tested by the application of an experiment. The retrospective design limits the level of evidence. Our findings have descriptive value and contributed to the foundation of clinical-relevant hypotheses that might be further investigated in an experimental study design. Emotional reactivity in patients with borderline personality disorder (BPD) due to dysfunctional processes is still a concept being developed[52,57]. We agree that a larger sample size would have been favorable. With a small sample we are limited to detecting big differences or big "effects" and our data need replication[58]. Further research should choose a larger sample size, to ensure sufficient power for extrapolating the results of any statistical analysis to the overall patient population. Of course, the design of an observational study with hot-spot recruitment should be replicated, which is currently under progress in our department. Replication seems not only necessary, but interesting, as other centers had found similar findings[59] especially concerning the dose-efficacy question and differences in high- and low-frequent settings: The more sessions took place with psychoanalytic technique, the better psycho-structural change could be achieved[59].

Very restricted resources often limit availability of psychotherapy in outpatient settings, despite the relevance of mental health problems. However, psychotherapy should be available for everyone with psychological strains and in need of treatment. In the outpatient clinic where this study took place, therapy places for borderline patients also with limited resources were available. Unfortunately, this might not be the usual terms.

CONCLUSION

Exploring the changes in patient characteristics and linking these changes to specific treatment strategies is of clinical importance not only when starting treatment but also for its long-term progress. The quality and accurate timing of patient-therapist interactions seem to be essential to change processes than the number of such interactions. During psychoanalytic treatments, therapy concomitant evaluations should be used to identify aspects of the therapy, that can either be promising for or preventive to a positive outcome and so that the therapist can accordingly adjust his/her intervention techniques. In therapy concomitant evaluations, the observation of repetitive interaction structures in connection to changes in patient characteristics should be a focus. By assessing the capability of therapists to interpret transferences appropriately, this instrument of a treatment concomitant evaluation could be used to assure the quality of psychoanalytic treatments. However, high-level evidence from meta-analysis regarding effects of psychological therapies for people with borderline personalities is still scant but benefits over TAU have been shown[60-63].

ARTICLE HIGHLIGHTS

Research background

Emotional reactivity in patients with borderline personality disorder (BPD) due to dysfunctional processes is still a concept being developed. Specifically designed psychotherapies for BPD have significant, modest benefits over TAU. The effects of psychotherapy on BPD are still insufficiently understood. Substantial heterogeneity of processes and populations studied contributes to varying research results when investigating the effects of different treatment methods, and whether they differ from each other.

Research motivation

The question was whether similarities and differences between psychoanalysis (PSA) and psychodynamic psychotherapy (PDT) in BPD would be detectable, especially in terms of emotional reactivity in the patient-therapist interaction.

Research objectives

We aimed to study repetitive interaction patterns in patients with BPD undergoing either psychoanalysis or psychodynamic therapy.

Research methods

Within a retrospective study framework, we compared matched PSA (n = 10) and PDT (n = 10) BPD patients' treatment sessions. Five consecutive sessions were recorded and analyzed, with evaluation of effects compared to baseline over three years. Patient characteristics (including affect regulation and personality traits), quality of object relations, as well as related therapeutic actions, were analyzed (micro-process analysis).

Research results

Differences between PSA and PDT were significant when analyzing the "mean change" in the Shedler-Westen Assessment Procedure Borderline variable after one year of therapy (P = 0.024). Variance of observed change was higher in PSA than in PDT (SD_{PSA} ± 9.29 *vs* SD_{PDT} ± 7.94). Transference interpretations are followed closely by affective changes in the patient, and were useful modes of interaction.

Research conclusions

PSA and PDT were both effective in BPD. Interactional aspects differed between the two treatments.

Research perspectives

As BPD patients are a very heterogeneous population, further research should focus on investigating optimal matching of BPD patients to specific modes of affect regulation, as well as which specific level of personality functioning would benefit from a given therapy modality.

ACKNOWLEDGEMENTS

The authors wish to express particular thanks to John Clarkin and Peter Fonagy for their help in initiating the study, Drew Westen and Enrico Jones for providing the rating instruments. We thank the external raters Katharina Hämmerle, Nora Frossard, Marion Swaton, Armina Hrusto-Lemes, Golda Schlaff and Simon Madanoglu. We also thank Hemma Rössler-Schülein for her help in gathering the data. The authors want to appreciate the contribution of Medical University of Vienna/General Hospital of Vienna and NÖ Landesgesundheitsagentur, legal entity of University Hospitals in Lower Austria, for providing the organizational framework to conduct this research.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1346-1365

DOI: 10.5498/wjp.v11.i12.1346

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Impact of lockdown relaxation and implementation of the face-covering policy on mental health: A United Kingdom COVID-19 study

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Author contributions: Rathod S, Rathod P and Phiri P developed the study protocol and questionnaire; Rathod S, Phiri P, Soomro MG, and Rahman MM contributed to the manuscript development; Rahman MM conducted the analysis; all authors reviewed and approved the final version of the manuscript.

Institutional review board statement: The study received ethics and HRA approval. IRAS project ID: 282858; REC reference: 20/HRA/1934 from London-Westminster Research Ethics Committee on 27 April 2020.

Informed consent statement: All study participants, provided informed consent prior to study enrollment.

Conflict-of-interest statement: Dr Rathod reports others from

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Abstract

BACKGROUND

Pandemic mitigation policies, such as lockdown, are known to impact on mental health of individuals. Compulsory face covering under relaxed lockdown restrictions gives assurance of less transmission of airborne infection and has the potential to improve mental health of individuals affected by restrictions.

AIM

To examine the association of the lockdown relaxation and the implementation of the face covering policy on the mental health of the general population and sub-groups in the United Kingdom using interrupted time series model.

METHODS

Using a web-based cross-sectional survey of 28890 United Kingdom adults carried out during May 1, 2020 to July 31, 2020, changes in mental health status using

Janssen, other from Otsuka, other from Lundbeck, outside the submitted work. Dr Phiri reports other from Queen Mary University London, other from Stanford University School of Medicine, other from John Wiley and Blackwell, outside the submitted work. All other authors report no conflict of interest.

Data sharing statement: Data will not be shared.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: United Kingdom

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: June 17, 2021
Peer-review started: June 17, 2021
First decision: July 14, 2021
Revised: August 4, 2021
Accepted: October 20, 2021

generalised anxiety disorder (GAD-7), and impact of events scale-revised (IES-R) scales are examined, at the dates of the first lockdown relaxation (July 4, 2020) and the subsequent introduction of face covering (July 24, 2020) in United Kingdom. A sharp regression discontinuity design is used to check discontinuities in mental health outcomes at policy-change dates.

RESULTS
Average GAD-7 scores of participants were 5.6, 5.6 and 4.3 during the lockdown period, the lockdown relaxation phase and the phase of compulsory face covering, respectively, with lower scores indicating lower anxiety levels. Corresponding scores for IES-R were 17.3, 16.8 and 13.4, with lower scores indicating less distress. Easing lockdown measures and subsequent introduction of face covering, on average, reduced GAD-7 by 0.513 (95%CI: 0.913-0.112) and 1.148 (95%CI: 1.800-0.496), respectively. Corresponding reductions in IES-R were 2.620 (95%CI: 4.279-0.961) and 3.449 (95%CI: 5.725-1.172). These imply that both lockdown relaxation and compulsory face-covering have a positive association with mental health scores (GAD-7 and IES-R).

CONCLUSION
The differential impact of lockdown and relaxation on the mental health of population sub-groups is evident in this study with future implications for policy. Introduction of face covering in public places had a stronger positive association with mental health than lockdown relaxation.

Key Words: COVID-19; Psychological impact; Lockdown; Face-covering; Mental health; Anxiety

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Core Tip: Positive association of lockdown relaxation and face-covering policies on the mental health (MH) of various population sub-groups is reported. Professional groups and health workers had lower generalised anxiety disorder (GAD-7) scores than other workers. During the compulsory face-covering phase, all professional groups improved on GAD-7 and impact of events scale-revised (IES-R) scores. Significant improvements in MH scores were found among non-key workers. Gender was associated with different MH outcomes during the lockdown, with females scoring higher on the GAD-7 and IES-R scales than males. However, both groups showed a significant improvement in MH status during the period of face-covering, with slightly higher improvements noted in males.

Citation: Rathod S, Pallikadavath S, Graves E, Rahman MM, Brooks A, Soomro MG, Rathod P, Phiri P. Impact of lockdown relaxation and implementation of the face-covering policy on mental health: A United Kingdom COVID-19 study. *World J Psychiatr* 2021; 11(12): 1346-1365
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1346.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1346

INTRODUCTION

Restriction of people's movements and interactions following wide-spread transmission of coronavirus disease 2019 (COVID-19) has been experienced by the global community. Several countries in the world have implemented lockdown measures to contain the spread of infection and/or delay the spread of infection in order to reduce mortality and morbidity.

The United Kingdom government implemented national lockdown in England on March 23, 2020. The restrictions imposed by the lockdown impacted on the health, economic and social welfare of individuals, households and society[1]. Lockdown reduced educational performance and nutrition of United Kingdom children caused by junk food intake[2]. Although it improved roadside air quality in the United

Article in press: October 20, 2021
Published online: December 19, 2021

P-Reviewer: Shawan DSA, Yu L
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

Kingdom because of the reduction of vehicles[3], there was £370 billion loss to the United Kingdom economy[4] in addition to the loss of human lives and health[5].

The lockdown measures were first relaxed on July 4, 2020 and further changes, primarily the compulsory use of face covering in shops, were introduced on July 24, 2020. Table 1 summarises relaxation measures and face covering policy introduced following lockdown on March 23, 2020. Policy makers and mental health care providers need to know the reliable estimates of such effects to target policies and services to mitigate the mental health impact of restrictive measures due to COVID-19.

Globally, there is evidence of mental health decline among the general population during the COVID-19 pandemic. China, Spain, Italy, Iran, the United States, Turkey, Nepal, and Denmark, reported relatively higher rates of symptoms of anxiety (6.33% to 50.9%), depression (14.6% to 48.3%), post-traumatic stress disorder (7% to 53.8%), psychological distress (34.43% to 38%), and stress (8.1% to 81.9%) among the general population[6]. Stay-at-home orders, greater reduction of social contacts and perceived changes in everyday life were the primary pathways to increased mental health problems[7].

In the United Kingdom, there is evidence of minor psychiatric disorders during the first month of lockdown. For example, generalized health questionnaire (GHQ-12) reported an increase of 0.48 (95%CI: 0.07–0.90) from 2018-19 to April, 2020[1]. Daly *et al* [8] also found a similar increase in GHQ-12 in the United Kingdom. The highest increases of GHQ-12 are seen among 18–24 years old (2.69 points, 95%CI: 1.89–3.48), 25–34 years old (1.57, 95%CI: 0.96–2.18), women (0.92, 95%CI: 0.50–1.35), and people living with young children (1.45, 95%CI: 0.79–2.12). The mental health of United Kingdom adults was slightly better at the early stages of lockdown than at the end of lockdown[9]. Suicidal thoughts increased during lockdown, especially among young United Kingdom adults[10]. However, the mental health effects of COVID-19 on United Kingdom healthcare professionals are ambiguous[11], and some studies found a positive impact of the pandemic on the mental health of this specific group in the United Kingdom[12,13]. A key limitation of these studies is that they did not undertake causal analyses, which is key for policy and programming. Further, there is a need to evaluate the impact of face covering policy on the mental health of different population sub-groups.

Altschul *et al*[14] captured associations of face-covering with the mental health of United Kingdom adults using the logit model and concluded that wearing face coverings more often does not negatively impact mental health. Mental health impact of face covering may be due to the confidence people felt, particularly those vulnerable, with regard to the protection it might offer from infection. Face covering was promoted with medical narrative[15] and hence its use was primarily seen as a medical intervention. It is important to understand whether such intervention provides mental health improvements. This paper addresses the research gap by trying to capture any associations of COVID-19 restrictions and their easing with key policies on the mental health of United Kingdom adults with special focus on population sub-groups. The authors used sharp regression discontinuity design (RDD) to analyse discontinuities in mental health outcomes at key policy-change dates. We also tested the key identification condition, the local randomization. If the factors affecting mental health outcomes were not found discontinuous at those cut-off dates, discontinuities in mental health outcomes were likely to be causal given other identification conditions (*e.g.*, unconfoundedness) hold[16]. There is no formal way of testing them, but this can be checked informally through falsification tests (*e.g.*, checking discontinuities in mental health outcomes at any false dates, checking false outcomes at lockdown policy changing dates). In this study, we consider the informal test through visual inspection of figures.

MATERIALS AND METHODS

Data

A cross-sectional online international survey of adults, 16 years and above, was carried out during May 1, 2020 to July 31, 2020 yielding a sample size of 28890 in England. Further details of the methodology are documented in an earlier publication by the group[13]. Of the total sample, 20174 completed the online questionnaire during lockdown; 4550 during the first phase of relaxation and 4145 during the face covering policy period.

Table 1 Lockdown relaxations in the United Kingdom

Date	Policy changes
July 4, 2020	2-metre distance rule was dropped
	Members of two different households have been able to drink or dine together
	Households will be able to host visitors, including overnight, and to meet with members of different households, on different occasions – including in a pub, restaurant or hotel, for example
	To reopen pubs, campsites, hairdressers, and churches. All these venues will be expected to collect and keep the contact details of visitors, so they can be traced in the event of a local outbreak of the virus
	Theatres and concert halls will also be able to reopen but they cannot host live performances because of concerns including the risk that singing can transmit the virus
July 24, 2020	Face mask has become compulsory in shops

Southern Health National Health Service (NHS) Foundation Trust co-ordinated the online survey with support from 50 NHS Trusts, Universities, and The Centre for Applied Research and Evaluation International Foundation. These organisations advertised the survey to their staff, patients and the general public with a weblink to the survey platform. Overall, more than 100 organizations were involved in sending the survey links to potential participants *via* professional routes and social media (Figure 1).

Study design

To study the impact of easing lockdown and introduction of face covering on mental health, both control and experimental groups are required. However, as the first United Kingdom lockdown was implemented at national level, there was no control group (*i.e.* areas without lockdown) available naturally within the nation to identify the impact of easing lockdown measures on mental health. In the absence of such control population, the RDD model is the most suitable method to address the objectives. As the United Kingdom lockdown and face covering policy had clear implementation protocols, including exact date and time, it was easier to identify cut-off points for policy change required for the chosen method. As far as we know there was no other policy announcement that might affect the mental health of the population to contaminate the effect. The two cut-off points (date of first lockdown easing and introduction of face covering) were July 4, 2020 and July 24, 2020, respectively. The RDD methodology allows for the creation of control and experimental groups by identifying populations with the same characteristics just before and after each cut-off date (*i.e.* July 4, 2020 and July 24, 2020). The population before the cut-off date serves as the control group and the after the cut-off date will be the experimental group. This creates two sets of control and experimental groups, one set at each cut-off date generating a quasi-experimental design.

The study received ethics and HRA approval. IRAS project ID: 282858; REC reference: 20/HRA/1934 from London-Westminster Research Ethics Committee on 27 April 2020.

Diagnostics

To test whether the data qualifies for RDD, predicted values of generalised anxiety disorder (GAD-7) and impact of events scale-revised (IES-R) are plotted against the interview end date (Figures 2 and 3). Vertical lines indicate cut-off dates. As data are highly scattered, figures without vertical lines (at the cut-off dates) and fitted lines will cause difficulty in understanding discontinuities at the cut-off dates. Predicted values are generated from regressions of these indices on the trend variable allowing discontinuities and changes in slopes. These predicted values pass through scatter points, which are daily averages of these indices. The interview end date is the date of completing the survey questionnaire by an individual. Interview end dates are used to make the trend variable (*e.g.*, 1 for first date, 2 for second date, *etc.*), and this gives the appropriate assignment variable. The two mental health measures show clear negative discontinuities at the first and second cut-off dates, implying that easing lockdown restrictions and introduction of face covering improved mental health.

Visual inspection of the two figures indicates slope changes after the first cut-off date. In survey data, such slope changes can be difficult to interpret. The analysis captures intercept discontinuities (steps) after also controlling for slope changes, as

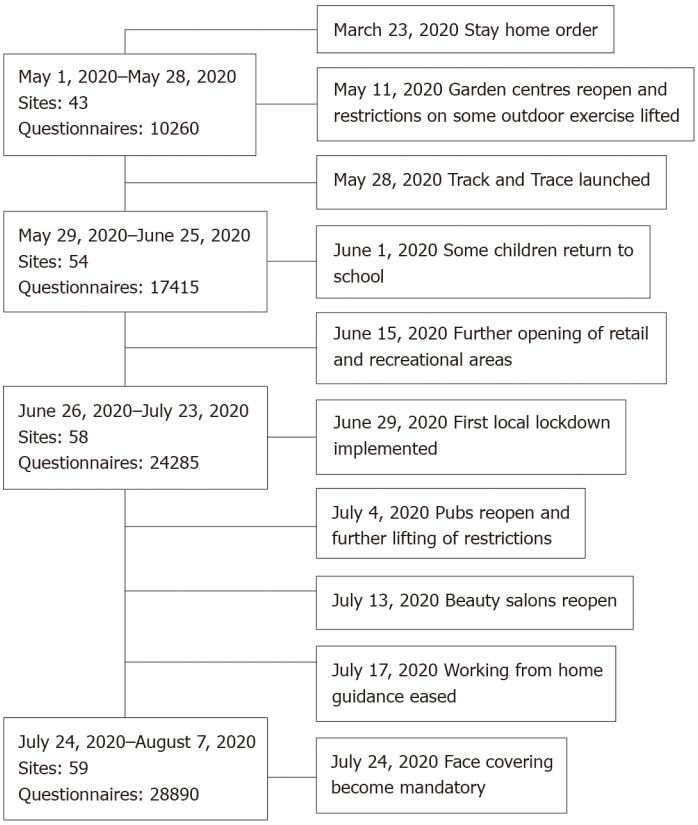


Figure 1 Survey recruitment and significant lockdown dates.

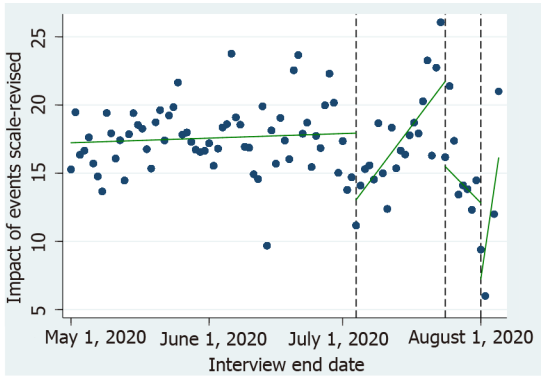


Figure 2 Discontinuities in impact of event scale-revised scale at two cut-off dates.

suggested by Angrist and Pischke[17] in RDD.

Modelling

The unit of analysis is an adult aged 16 years or over. The outcome of interest, mental health outcome measured using GAD-7 and IES-R, is denoted by Y, which varies across different groups of individuals (*e.g.*, health *vs* non-health workers, male *vs* female, *etc.*) by date. For purposes of regression, date is used as the trend variable, which contains 1 for the first date, 2 for the second date, and so on. Individual and time are indicated by i and t, respectively. As mental health conditions change around the cut-off time, the following RDD type of interrupted time series model was used:

$$Y_{it} = \alpha + \beta_1 d_{t1} + \beta_2 d_{t2} + \beta_3 d_{t1}(Trend_t\text{-}c_1) + \beta_4 d_{t2}(Trend_t\text{-}c_2) + \beta_5(Trend_t\text{-}c_1) + X_{it}\theta + \epsilon_{it}$$

where α is the constant term, d_{t1} = *1{Interview end date* ≥ 4th *of July}*, and d_{t2} = *1{Interview end date* ≥ 24th *of July}* are discontinuity dummies, c_1 = *Value of trend for the date of* 4th *of July* and c_1 = *Value of trend for the date of* 24th *of July* the two cut-off points, X_{it} is the row vector of control variables (listed in Tables 2 and 3) and θ is the column vector of their coefficients, and $\in_{it}$ is the error term. β_1 and β_2 are parameters of discon-

Table 2 Sampling distribution of mental health outcomes, demographics, lifestyle changes, and pre-existing health conditions by lockdown periods

Time by lockdown easing policy	May 1, 2020-July 3, 2020 (Lockdown phase)		July 4-23, 2020 (Lockdown relaxation phase)		July 24-31, 2020 (Face-covering phase)		Total		
Outcome and control variables	No.	%	No.	%	No.	%	No.	%	*P* value
Total sample	20173	100	4550	100	4145	100	28890	100	
Mental health outcomes/scores									
GAD-7									
Total	15634	100	3379	100	3153	100	22166	100	
Missing	4539		1171		992		6711		
IES-R									
Total	14516	100	3141	100	2961	100	20618	100	
Missing	5657		1409		1184		8260		
Demographics, lifestyle changes, and pre-existing health conditions									
Key worker									
No	5400	29.7	1260	31.4	1778	48.8	8438	32.6	
Yes (health)	9205	50.6	1961	48.9	1161	31.8	12327	47.7	
Yes (non-health)	3595	19.8	793	19.8	708	19.4	5096	19.7	
Total	18200	100	4014	100	3647	100	25861	100	< 0.001
Missing	1973		536		498		3014		
Gender									
Female	15324	84.2	3331	83.4	2701	75.2	21356	82.8	
Male	2872	15.8	662	16.6	891	24.8	4425	17.2	
Total	18196	100	3993	100	3592	100	25781	100	< 0.001
Missing	1977		557		553		3094		
Age category or group									
Under 21	332	1.8	90	2.2	81	2.2	503	1.9	
21-24	828	4.5	163	4	100	2.7	1091	4.2	
25-34	3627	19.8	709	17.5	566	15.4	4902	18.8	
35-44	4076	22.2	794	19.5	712	19.4	5582	21.4	
45-54	4676	25.5	1008	24.8	851	23.2	6535	25.1	
55-64	3462	18.9	882	21.7	795	21.6	5139	19.7	
65 and over	1319	7.2	416	10.2	568	15.5	2303	8.8	
Total	18320	100	4062	100	3673	100	26055	100	< 0.001
Missing	1853		488		472		2820		
Ethnicity									
Non-white British	1649	9	362	8.9	351	9.5	2362	9.1	
White British	16703	91	3698	91.1	3325	90.5	23726	90.9	
Total	18352	100	4060	100	3676	100	26088	100	< 0.001
Missing	1821		490		469		2787		
Religion									
Non-Christian	9794	54.1	2140	54.3	1905	53.8	13839	54.1	
Christian	8306	45.9	1798	45.7	1633	46.2	11737	45.9	

Total	18100	100	3938	100	3538	100	25576	100	0.911
Missing	2073		612		607		3300		
Age left education									
≤ 18 (A-level or less)	5967	33	1557	38.9	1249	34.4	8773	34.1	
> 18 (Higher degree)	12118	67	2442	61.1	2381	65.6	16941	65.9	
Total	18085	100	3999	100	3630	100	25714	100	
Missing	2088		551		515		3161		
Accommodation									
Rented home	5030	27.5	1163	28.7	847	23	7040	27	
Own home	13288	72.5	2891	71.3	2834	77	19013	73	
Total	18318	100	4054	100	3681	100	26053	100	< 0.001
Missing	1855		496		464		2822		
Vulnerable according to government category									
No	13735	80.6	2938	78.5	2610	77.7	19283	79.8	
Yes (do not require shielding)	2005	11.8	503	13.4	494	14.7	3002	12.4	
Yes (require shielding)	1307	7.7	303	8.1	257	7.6	1867	7.7	
Total	17047	100	3744	100	3361	100	24152	100	< 0.001
Missing	3126		806		784		4725		
Experienced coronavirus									
No	4354	24.9	1016	26.3	971	27.8	6341	25.5	
Yes	13152	75.1	2843	73.7	2518	72.2	18513	74.5	
Total	17506	100	3859	100	3489	100	24854	100	0.001
Missing	2667		691		656		4022		
Pre-existing mental health condition									
No	10685	62.6	2288	60.8	2404	70.1	15377	63.3	
Yes	6395	37.4	1476	39.2	1026	29.9	8897	36.7	
Total	17080	100	3764	100	3430	100	24274	100	< 0.001
Missing	3093		786		715		4604		
Drinking alcohol									
Never	2611	14.6	540	13.7	492	13.8	3643	14.4	
Monthly or less	3954	22.2	944	24	692	19.4	5590	22.1	
2-4 times a month	3909	21.9	930	23.6	824	23	5663	22.3	
2-3 times a week	4873	27.3	1007	25.6	999	27.9	6879	27.1	
4 times or more a week	2479	13.9	520	13.2	569	15.9	3568	14.1	
Total	17826	100	3941	100	3576	100	25343	100	< 0.001
Missing	2347		609		569		3532		
Taking drug									
No	17354	97.9	3810	97.3	3465	97.3	24629	97.7	
Yes	369	2.1	107	2.7	95	2.7	571	2.3	
Total	17723	100	3917	100	3560	100	25200	100	< 0.001
Missing	2450		633		585		3675		
Suicidal thoughts									

No	12015	68.3	2591	66.7	2521	71.5	17127	68.5	
Yes	5572	31.7	1292	33.3	1005	28.5	7869	31.5	
Total	17587	100	3883	100	3526	100	24996	100	< 0.001
Missing	2586		667		619		3879		

GAD-7: Generalised anxiety disorder-7; IES-R: Impact of events scale-revised.

tinuities at two respective cut-off dates, and β_3 and β_4, are parameters of kinks (slope changes) at two respective cut-off dates. Parameters of interest in this paper are discontinuity parameters, β_1 and β_2, which give changes in mental health scores at the two cut-off dates.

The control variables included in the analysis are socio-demographic characteristics (*e.g.*, profession, age, ethnicity, religion, gender, education, accommodation, *etc.*), lifestyle characteristics (*e.g.*, experiencing coronavirus, drug use, drinking alcohol, *etc.*), and pre-existing health conditions (*e.g.*, vulnerability, suicidal thoughts, mental health conditions). The outcome variable of interest is mental health status. Two widely used standardized measures have been used to measure levels of anxiety (GAD-7)[18], and subjective distress (IES–R)[19]. The GAD-7 ranges from 0 to 21, and it categorizes as minimal (0-4), mild (5-9), moderate (10-14), and severe (15-21). The IES-R ranges from 0 to 88, and it categorizes as minimal (0-23), post-traumatic stress disorder (PTSD) may be a concern (24-32), probable PTSD diagnosis (33-38), and high PTSD (39-88). A total of 22,166 respondents completed the GAD-7 questionnaire. Of those 15634 were completed during lockdown, 3379 during the first phase of lockdown relaxation, and 3153 during the face covering phase. A total of 20618 respondents completed the IES-R questionnaire, 14516 respondents completed this during lockdown, 3141 during the first phase and 2961 during the second phase of lockdown relaxation.

Table 2 presents percentage distribution of control variables used in the regressions according to lockdown, lockdown relaxation, and face covering implementation period. It suggests that the proportions of control variables in the three time periods follow a similar pattern. However, there are higher proportions of health workers (31.8%-50.6%) and females (75.2%-84.2%) in the sample. The table shows that (P < 0.001) percentages of control variables vary significantly during each of the time periods. Such discrepancies in demographic characteristics of respondents will not violate identification conditions as discrepancies of those covariates do not exist around the cut-off dates in most cases (*e.g.*, the existence of local randomization available in supplementary material). The table also shows missing values, which are unlikely to make any serious impact on the results of regressions as the individuals are distributed based on comparable characteristics before and after the cut-off dates.

RESULTS

Mental health outcomes by background characteristics

Table 3 provides average scores of the two mental health measures for three time periods: During lockdown; during relaxation and the face covering period. Comparisons of the average scores between these time periods gives us raw estimates of the effects of the lockdown relaxation and the compulsory face covering policies. The average scores of GAD-7 and IES-R at the three time periods suggest that the mental health of the respondents was worse during lockdown but has improved after the lockdown easing and during the period of face covering. For example, the overall mean GAD-7 scores were 5.6 each for the lockdown period and the first phase of lockdown relaxation, compared to 4.4 during the period of face covering. For the IES-R, the average scores were 17.3, 16.8 and 13.4 for the periods of lockdown, lockdown relaxation, and face covering, respectively, suggesting a reduction in anxiety and distress during the first relaxation, but significant reductions were noticed during the period of face-covering.

There were notable differences in the associations of lockdown relaxation and compulsory face covering policies on mental health of various population sub-groups. Among the professional groups, health workers had the lowest GAD-7 score (5.1) compared to other key workers (6.3) and non-key workers (5.8) during the lockdown period. Similar findings were observed for the IES-R, 18.5 for non-key workers, 15.9 for health workers and 19.0 for other key workers. During the compulsory face covering

Table 3 Means of mental health conditions by lockdown easing periods, demographics, lifestyle changes, and pre-existing health conditions

Control variables	Means of GAD-7 (*n* = 18948) (95%CI)			Means of IES-R (*n* = 17739) (95%CI)		
	May 1, 2020-July 3, 2020 (Lockdown)	July 4-23, 2020 (Lockdown relax)	July 24-31, 2020 (Face-covering)	May 1, 2020-July 3, 2020 (Lockdown)	July 4-23, 2020 (Lockdown relax)	July 24-31, 2020 (Face-covering)
Total study population	5.6 (5.5-5.7)	5.6 (5.3-5.8)	4.4 (4.2-4.6)	17.3 (16.9-17.6)	16.8 (16.0-17.6)	13.4 (12.7-14.2)
Key worker						
Not a key worker	5.8 (5.6-6.0)	6.2 (5.7-6.7)	4.1 (3.8-4.4)	18.5 (17.8-19.2)	19.9 (18.2-21.5)	13.1 (12.1-14.2)
Health	5.1 (5.0-5.3)	5 (4.7-5.3)	4.3 (3.9-4.6)	15.9 (15.4-16.3)	14.4 (13.4-15.4)	12.2 (11.0-13.5)
Not in health	6.3 (6.1-6.6)	6.1 (5.5-6.6)	5.3 (4.8-5.9)	19 (18.2-19.8)	18.5 (16.8-20.3)	16.1 (14.4-17.9)
Gender						
Female	5.8 (5.7-5.9)	5.7 (5.5-6.0)	4.8 (4.5-5.1)	18 (17.6-18.4)	17.3 (16.4-18.2)	14.4 (13.5-15.2)
Male	4.3 (4.0-4.5)	4.8 (4.1-5.4)	3.2 (2.8-3.7)	13.3 (12.4-14.1)	14.1 (12.2-16.1)	10.7 (9.4-12.1)
Age group						
Under 21	7.7 (6.8-8.5)	9.3 (6.7-11.9)	8.6 (6.4-10.9)	24 (20.9-27.1)	30.8 (20.8-40.8)	28.8 (20.2-37.3)
21-24	7.9 (7.4-8.5)	7.8 (6.3-9.2)	6.7 (5.0-8.4)	22.6 (20.8-24.3)	21.4 (17.0-25.7)	19.2 (13.9-24.5)
25-34	6.8 (6.5-7.0)	7.5 (7.0-8.1)	5.7 (5.1-6.4)	19 (18.2-19.8)	21.3 (19.4-23.2)	15.4 (13.3-17.4)
35-44	6.1 (5.9-6.3)	6.1 (5.6-6.6)	5.2 (4.7-5.7)	18.3 (17.5-19.0)	17.8 (16.1-19.5)	14.4 (12.8-15.9)
45-54	4.9 (4.7-5.1)	4.8 (4.4-5.3)	4.5 (4.0-5.0)	16.2 (15.6-16.9)	14.5 (13.0-16.0)	13.2 (11.8-14.7)
55-64	4.6 (4.4-4.8)	4.8 (4.3-5.3)	3.7 (3.3-4.1)	15.7 (15.0-16.5)	14.8 (13.2-16.4)	12.6 (11.2-14.0)
65 and over	3.1 (2.8-3.4)	3.1 (2.5-3.7)	1.9 (1.4-2.3)	10.8 (9.7-11.8)	12.2 (9.7-14.6)	8.1 (6.5-9.7)
Ethnicity						
Non-white	4.9 (4.5-5.2)	5.9 (5.1-6.8)	4.9 (4.1-5.7)	15.9 (14.7-17.1)	19.2 (16.3-22.0)	14.4 (12.0-16.8)
White	5.6 (5.5-5.7)	5.5 (5.3-5.8)	4.4 (4.1-4.6)	17.4 (17.0-17.7)	16.6 (15.7-17.4)	13.3 (12.5-14.1)
Religion						
Non-Christian	5.7 (5.6-5.9)	6.0 (5.6-6.3)	4.6 (4.3-4.9)	17.6 (17.2-18.1)	17.6 (16.5-18.7)	13.8 (12.8-14.8)
Christian	5.4 (5.2-5.5)	5.1 (4.8-5.5)	4.2 (3.9-4.5)	16.8 (16.3-17.3)	15.8 (14.6-17.0)	12.9 (11.9-14.0)
Education						
A-level or less	6.2 (6.0-6.4)	6.1 (5.7-6.6)	4.5 (4.1-4.9)	19.1 (18.4-19.8)	19.1 (17.6-20.5)	14.3 (12.9-15.7)
Higher degree	5.3 (5.2-5.4)	5.2 (4.9-5.5)	4.4 (4.1-4.6)	16.4 (16.0-16.8)	15.5 (14.6-16.4)	13 (12.2-13.9)
Type of accommodation						
Rented	7.1 (6.9-7.3)	7.8 (7.3-8.3)	6.7 (6.1-7.3)	21.6 (20.9-22.3)	23.1 (21.4-24.8)	19.7 (17.8-21.6)
Own	5 (4.9-5.1) 4	4.7 (4.5-5.0)	3.8 (3.5-4.0)	15.7 (15.3-16.0)	14.4 (13.5-15.3)	11.7 (10.9-12.4)
Shielding status (government)						
Shielding not required	5.5 (5.4-5.6)	5.5 (5.2-5.8)	4.4 (4.1-4.6)	16.8 (16.5-17.2)	16.2 (15.3-17.1)	12.9 (12.1-13.7)
Shielding required (but not Shielding)	5.5 (5.2-5.9)	5.1 (4.5-5.8)	4 (3.4-4.6)	17.6 (16.5-18.6)	16.6 (14.5-18.8)	13 (11.0-14.9)
Shielding required (shielding)	6.6 (6.2-7.0)	7.4 (6.4-8.5)	5.5 (4.6-6.5)	21.2 (19.8-22.6)	23.9 (20.7-27.2)	19.3 (16.2-22.3)
Experience of COVID-19						
No such experience	5.1 (4.9-5.3)	5.1 (4.6-5.6)	3.9 (3.5-4.4)	15.5 (14.8-16.2)	16.3 (14.7-18.0)	12.1 (10.7-13.5)
Yes	5.7 (5.6-5.8)	5.7 (5.4-6.0)	4.6 (4.3-4.9)	17.8 (17.4-18.2)	17 (16.1-17.9) 1	3.9 (13.1-14.8)
Pre-existing mental health						

No	4.1 (4.0-4.2)	3.7 (3.5-3.9)	3.2 (2.9-3.4)	13 (12.6-13.3)	11.5 (10.7-12.3)	9.7 (9.0-10.4)
Yes	8.2 (8.0-8.4)	8.7 (8.3-9.2)	7.6 (7.1-8.1)	24.9 (24.3-25.6)	25.9 (24.5-27.4)	23 (21.3-24.7)
Drinking alcohol						
Never	6.3 (6.0-6.6)	6.2 (5.5-6.9)	5.7 (4.9-6.4)	19.7 (18.6-20.7)	17.9 (15.6-20.2)	16.2 (13.8-18.6)
Monthly or less	6.2 (6.0-6.5)	6.6 (6.0-7.1)	5 (4.4-5.5)	18.8 (18.0-19.6)	19.5 (17.6-21.3)	15.2 (13.4-17.0)
2-4 times a month	5.4 (5.2-5.6)	5.3 (4.8-5.8)	4.3 (3.8-4.7)	16.7 (15.9-17.4)	17 (15.4-18.5)	13 (11.5-14.5)
2-3 times a week	5 (4.9-5.2) 5	5.2 (4.7-5.6)	3.9 (3.5-4.4)	15.5 (14.9-16.1)	15.2 (13.7-16.7)	12.2 (10.9-13.5)
4 times or more a week	5.1 (4.8-5.3)	4.3 (3.7-5.0)	3.8 (3.2-4.4)	16.9 (16.0-17.9)	13.4 (11.6-15.3)	12 (10.3-13.7)
Drug use						
Never	5.5 (5.4-5.6)	5.5 (5.2-5.7)	4.3 (4.1-4.6)	17.1 (16.8-17.5)	16.6 (15.8-17.4)	13.1 (12.4-13.9)
Ever	7.7 (6.8-8.6)	9.6 (7.9-11.4)	7.3 (5.5-9.1)	23.8 (20.9-26.8)	25.5 (19.9-31.1)	24.2 (18.3-30.0)
Suicidal thoughts ever						
No	4.5 (4.4-4.6)	4.4 (4.1-4.7)	3.4 (3.2-3.7)	13.9 (13.5-14.3)	13.2 (12.3-14.0)	10.3 (9.6-11.0)
Yes	7.8 (7.6-8.0)	8 (7.6-8.5)	6.9 (6.4-7.4)	24.3 (23.7-25.0)	24.4 (22.8-25.9)	21.6 (19.9-23.3)

CI: Confidence intervals; COVID-19: Coronavirus disease 2019; GAD-7: Generalised anxiety disorder-7; IES-R: Impact of events scale-revised.

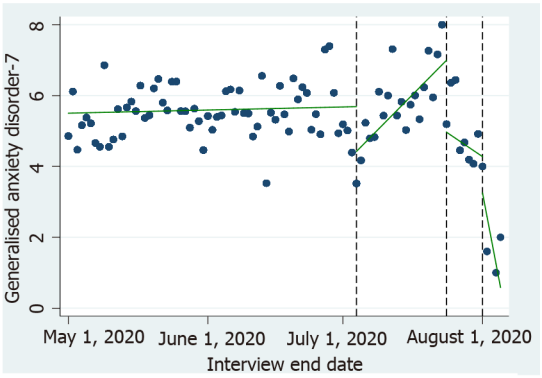


Figure 3 Discontinuities in generalised anxiety disorder-7 scale at two cut-off dates.

phase, there were improvements (mean reductions) in both mean scores for all three professional groups; the GAD-7 and IES-R scores were 4.1 and 13.1 for non-key workers, 4.3 and 12.2 for health workers, and 5.3 and 16.1 for non-health workers during the period of face covering, respectively. These imply that greater improvements in mental health are found among non-key workers than key workers, meaning that non-key workers were affected more by COVID-19. However, the regression results give a better indication.

In this study, gender was associated with mental health outcomes. During the lockdown, females had higher GAD-7 mean scores (5.8) compared to males (4.3). A similar pattern was observed for the IES-R (18.00 for females and 13.3 males). Both groups have shown significant improvements in anxiety and distress during the period of face covering, but slightly higher improvements are seen among males compared to females.

Table 3 further shows that both GAD-7 and IES-R were higher among younger age groups. For example, during lockdown, GAD-7 score was 7.7 for the under 21 years age group compared to 3.1 for the 65+ age group. The IES-R was 24.00 for the below 21 years age group compared to 10.8 for the 65+ age group. Both the scores of all age groups have declined during the face covering period. Compared to the middle age groups (*e.g.*, 35-44, 45-54), higher reductions (at least in terms of percentage) are seen among the lower and higher age groups.

Ethnic variations in mental health were also noted in this study. White ethnic population had higher GAD-7 (5.6) and IES-R (17.4) scores during the lockdown period compared to non-white (GAD-7, 4.9; IES-R, 15.9) ethnic group. Both ethnic groups showed notable improvements in average GAD-7 and IES-R scores at the face covering period, but not during the lockdown relaxation period. The white group shows greater improvements in mental health than the non-white group. Among non-Christians, both GAD-7 (5.7) and IES-R (17.6) scores were higher compared to Christians (GAD-7, 5.4; IES-R, 16.8). Similar to ethnicity, notable improvements in the average anxiety and distress scores of the two measures were noted in the face covering period, but not for the lockdown relaxation period. Slightly greater improvements in mental health are seen among Christians (who are mainly white ethnic population) than non-Christians.

Educational differences in mental health status by lockdown status and face covering were found in this study. During lockdown, average mental health scores for the two measures were higher for those with A-level or less (GAD-7, 6.2; IES-R, 19.1) compared to those with degree qualification (GAD-7, 5.3; IES-R, 16.4). Although there were some improvements in the mental health scores during the first lockdown relaxation, larger improvements were noted in the face covering period. In the face covering period, larger falls in both scores are seen among lower educated groups, implying that this group of educated people that includes lower-skilled workers was possibly hit more by COVID-19. Those who lived in rental accommodation during lockdown experienced more distress, with higher scores for both GAD-7 (7.1) and IES-R (21.6) compared to those living in their own homes (GAD-7, 5.0; IES-R, 15.7). Notable improvements in both GAD-7 and IES-R scores were found in the face covering period, and greater improvements are seen for those who live in their own houses.

During the lockdown period, those who shielded as *per* government advice had higher mental health scores for the two measures (GAD-7 = 6.6; IES-R = 21.2) compared to those who did not shield although they were advised to shield (GAD-7 = 5.5; IES-R = 17.6). Again, improvements in mental health of both groups are seen during the face covering period, but greater improvements are seen among those who shielded. Those who have experienced some COVID-19 related unpleasant experiences, had higher anxiety and distress scores (GAD-7 = 5.7; IES-R = 17.8 during the lockdown phase) compared to those who did not experience such situations (GAD-7 = 5.1; IES-R = 15.5 during the lockdown phase). Their mental health status improved significantly when the face covering policy was introduced. Greater improvement is seen among individuals who experienced coronavirus in IES–R scores. Similarly, those who had pre-existing mental health problems had higher mental health scores in both GAD-7 and IES-R in all three phases. Again, they experienced lower mental health problems after the face covering policy was introduced, but individuals without pre-existing mental health conditions experienced greater mental health improvements during the face covering phase.

In all three phases, those who never drank alcohol had higher anxiety and distress scores compared to those who reported alcohol consumption four or more times a week. Implementation of the face covering policy improved mental health scores of all groups of alcohol users. Users of drugs had higher anxiety and distress scores compared to 'never' users, but never users of drugs showed higher improvements in mental health scores during the face covering phase. Those who ever experienced suicidal thoughts had higher anxiety and distress scores compared to those who never had such thoughts. As with all other factors, improvements were noted when the face covering policy was introduced, but again, greater improvements are seen among the non-vulnerable group, those who never experienced suicidal thoughts.

Results from regression models

Table 4 shows the changes in mental health outcomes measured using GAD-7 and IES-R by two policy changes dates (July 4 and 24, 2020), and demographics, pre-existing health conditions, and lifestyles. For every group of demographics, pre-existing health conditions, and lifestyles, changes in anxiety and distress scores at two dates were estimated by running a simple OLS regression, which followed the specification of the interrupted time series model equation. The coefficients of two discontinuity dummies for two policy changes dates, which are estimates of changes in anxiety and distress scores at two dates, are shown in the Table 4. In each regression, linear function of trend variable (time) was considered, as Figures 2 and 3 did not suggest any non-linearity. To note that, in the regression of a group, all other covariates except one corresponding to that group were used. For example, in the regression of the male group, the only male dummy was dropped, but all other covariates defined by all

Table 4 Changes in mental health indices by cut-off dates, control variables from regression discontinuity design regression models

Policy change dates in 2020	Population sub-groups	GAD-7, changes (95%CI)	*P* value	IESR, changes (95%CI)	*P* value
July 4, 2020 (Lockdown relaxation date)	Total sample	-0.513 (-0.913, -0.112)	0.081	-2.620 (-4.279, -0. 961)	0.464
July 24, 2020 (Face-covering start date)	Total sample	-1.148 (-1.800, -0.496)		-3.449 (-5.725, -1.172)	
	Key worker				
July 4, 2020 (Lockdown relaxation date)	Not a key worker	-0.910 (-1.810, -0.011)	0.062	-3.546 (-6.235, -0.857)	0.708
	Health	0.017 (-0.602, 0.637)		-1.643 (-3.914, 0.628)	
	Non-health	-0.756 (-1.877, 0.365)		-1.704 (-5.115, 1.708)	
July 24, 2020 (Face-covering start date)	Not a key worker	-1.191 (-2.259, -0.123)	0.064	-3.877 (-7.410, -0.343)	0.843
	Health	-0.986 (-1.584, -0.387)		-1.693 (-4.376, 0.991)	
	Non-health	-1.421 (-3.454, 0.613)		-5.458 (-9.144, -1.772)	
	Gender				
July 4, 2020 (Lockdown relaxation date)	Female	-0.496 (-0.983, -0.010)	0.817	-2.606 (-4.445, -0.767)	0.936
	Male	-0.622 (-1.652, 0.409)		-2.461 (-5.929, 1.007)	
July 24, 2020 (Face-covering start date)	Female	-1.013 (-1.778, -0.248)	0.382	-3.369 (-5.789, -0.948)	0.926
	Male	-1.739 (-2.993, -0.485)		-3.112 (-6.985, 0.762)	
	Age group				
July 4, 2020 (Lockdown relaxation date)	Under 21	-5.482 (-9.526, -1.437)	0.029	-19.319 (-41.541, 2.902)	0.260
	21-24	-0.103 (-1.975, 1.770)		-3.715 (-8.350, 0.920)	
	25-34	-0.314 (-1.346, 0.717)		-2.653 (-4.900, -0.406)	
	35-44	-0.640 (-1.646, 0.366)		0.545 (-2.309, 3.399)	
	45-54	0.179 (-0.663, 1.021)		-1.871 (-4.785, 1.043)	
	55-64	-0.911 (-2.117, 0.294)		-5.390 (-9.419, -1.361)	
	65 and over	-0.923 (-2.330, 0.484)		-2.633 (-8.466, 3.199)	
July 24, 2020 (Face-covering start date)	Under 21	-0.983 (-5.502, 3.536)		-3.941 (-23.634, 15.753)	
	21-24	-0.830 (-6.322, 4.661)		-2.354 (-14.469, 9.761)	
	25-34	-1.928 (-3.272, -0.584)		-7.306 (-11.582, -3.029)	
	35-44	-0.722 (-2.406, 0.962)		-0.469 (-5.717, 4.780)	
	45-54	-0.641 (-1.940, 0.658)		-2.386 (-5.752, 0.980)	
	55-64	-0.997 (-1.971, -0.023)		-1.930 (-5.331, 1.472)	
	65 and over	-1.447 (-2.952, 0.057)	0.995	-4.192 (-9.646, 1.261)	0.795
	Ethnicity				
July 4, 2020 (Lockdown relaxation date)	Non-white	1.302 (0.085, 2.518)		3.185 (-2.139, 8.510)	
	White	-0.657 (-1.129, -0.185)	0.018	-3.044 (-4.830, -1.259)	0.035
July 24, 2020 (Face-covering start date)	Non-white	-0.104 (-1.715, 1.506)		-0.380 (-6.308, 5.548)	
	White	-1.243 (-1.957, -0.529)	0.348	-3.567 (-5.888, -1.246)	0.410
	Religion				

July 4, 2020 (Lockdown relaxation date)	Non-Christian	-0.369 (-0.934, 0.195)	0.522	-2.500 (-4.563, -0.437)	0.904
	Christian	-0.652 (-1.298, -0.006)		-2.679 (-4.909, -0.449)	
July 24, 2020 (Face-covering start date)	Non-Christian	-1.298 (-2.290, -0.306)	0.578	-3.473 (-6.483, -0.464)	0.957
	Christian	-0.928 (-1.630, -0.226)		-3.354 (-6.289, -0.420)	
	Education				
July 4, 2020 (Lockdown relaxation date)	A-level or less	-1.363 (-1.929, -0.797)	0.007	-3.958 (-6.641, -1.275)	0.221
	Higher degree	-0.080 (-0.512, 0.352)		-1.955 (-3.408, -0.502)	
July 24, 2020 (Face-covering start date)	A-level or less	-1.421 (-2.058, -0.783)	0.460	-4.109 (-6.780, -1.438)	0.561
	Higher degree	-0.876 (-1.712, -0.041)		-2.667 (-5.356, 0.022)	
	Accommodation				
July 4, 2020 (Lockdown relaxation date)	Rented	-0.369 (-1.449, 0.712)	0.796	-1.933 (-5.935, 2.068)	0.675
	Own	-0.517 (-0.919, -0.114)		-2.719 (-4.784, -0.653)	
July 24, 2020 (Face-covering start date)	Rented	-1.837 (-3.056, -0.618)	0.197	-4.387 (-9.165, 0.391)	0.571
	Own	-0.782 (-1.419, -0.144)		-2.820 (-4.892, -0.748)	
	Require shielding by government				
July 4, 2020 (Lockdown relaxation date)	Not required	-0.322 (-0.750, 0.107)	0.241	-2.212 (-3.717, -0.706)	0.560
	Required shielding, but not shielding	-1.243 (-2.295, -0.191)		-4.136 (-8.303, 0.032)	
	Required shielding and shielding	-0.655 (-2.023, 0.713)		-3.447 (-8.512, 1.619)	
July 24, 2020 (Face-covering start date)	Not required	-0.978 (-1.721, -0.234)	0.393	-3.175 (-5.683, -0.668)	0.956
	Require shielding, but not shielding	-1.045 (-2.351, 0.261)		-3.730 (-10.106, 2.647)	
	Require shielding and shielding	-3.064 (-4.686, -1.442)		-4.742 (-10.111, 0.628)	
	Experience of COVID-19				
July 4, 2020 (Lockdown relaxation date)	No	-0.559 (-1.279, 0.161)	0.892	-1.999 (-4.771, 0.774)	0.657
	Yes	-0.490 (-0.961, -0.018)		-2.795 (-4.666, -0.924)	
July 24, 2020 (Face-covering start date)	No	-1.927 (-2.904, -0.951)	0.156	-6.223 (-10.542, -1.905)	0.131
	Yes	-0.875 (-1.621, -0.129)		-2.462 (-4.509, -0.416)	
	Pre-existing mental health condition				
July 4, 2020 (Lockdown relaxation date)	No	-0.343 (-0.729, 0.043)	0.551	-2.308 (-3.782, -0.834)	0.788
	Yes	-0.649 (-1.582, 0.284)		-2.772 (-6.246, 0.702)	
July 24, 2020 (Face-covering start date)	No	-0.687 (-1.194, -0.181)	0.239	-1.407 (-3.154, 0.340)	0.056
	Yes	-1.576 (-3.163, 0.012)		-6.239 (-10.192, -2.286)	
	Drinking alcohol				
July 4, 2020 (Lockdown relaxation date)	Never	-1.025 (-2.463, 0.412)		-3.091 (-7.778, 1.596)	
	Monthly or less	-0.582 (-1.779, 0.615)		-3.020 (-6.621, 0.581)	

	2-4 times a month	-0.243 (-0.901, 0.415)		-2.017 (-4.434, 0.401)	
	2-3 times a week	-0.050 (-0.543, 0.443)		-1.782 (-3.882, 0.319)	
	4 times or more a week	-1.165 (-2.178, -0.151)	0.401	-3.784 (-7.229, -0.340)	0.828
July 24, 2020 (Face-covering start date)	Never	-1.309 (-3.955, 1.337)	0.835	2.636 (-2.839, 8.111)	0.607
	Monthly or less	-1.240 (-2.787, 0.306)		-2.619 (-5.693, 0.455)	
	2-4 times a month	-1.251 (-2.243, -0.259)		-6.981 (-10.394, -3.568)	
	2-3 times a week	-1.140 (-1.694, -0.587)		-4.444 (-7.173, -1.715)	
	4 times or more a week	-0.601 (-2.269, 1.067)		-1.616 (-6.815, 3.583)	
	Taking drugs				
July 4, 2020 (Lockdown relaxation date)	No	-0.504 (-0.890, -0.118)	0.542	-2.522 (-4.160, -0.883)	0.955
	Yes	0.631 (-3.023, 4.286)		-2.827 (-12.067, 6.412)	
July 24, 2020 (Face-covering start date)	No	-1.114 (-1.669, -0.558)	0.875	-3.571 (-5.538, -1.604)	0.222
	Yes	-1.470 (-6.338, 3.398)		5.805 (-11.429, 23.039)	
	Suicidal thoughts ever				
July 4, 2020 (Lockdown relaxation date)	No	-0.173 (-0.599, 0.252)	0.039	-0.941 (-2.482, 0.600)	0.003
	Yes	-1.232 (-1.983, -0.481)		-5.938 (-8.759, -3.118)	
July 24, 2020 (Face-covering start date)	No	-0.831 (-1.343, -0.319)	0.337	-2.520 (-4.065, -0.975)	0.511
	Yes	-1.588 (-3.487, 0.310)		-4.256 (-9.486, 0.974)	

Note: To capture the effects of lockdown easing and compulsory face-covering on different groups, separate OLS regressions were run for all demographics, lifestyle change type, and pre-existing health condition (listed above) using the Regression Discontinuity Design model. Cluster/date/trend adjusted 95% confidence intervals are in parentheses. *P* values are shown to indicate whether changes in mental health scores are different among those listed groups. CI: Confidence intervals; COVID-19: Coronavirus disease 2019; GAD-7: Generalised anxiety disorder-7; IES-R: Impact of events scale-revised.

other groups are used.

Compared to discontinuities seen in Figures 2 and 3, the smaller discontinuities in outcomes are due to controlling for the effects of a large set of individual risk factors. This should be obvious as the regressions control for individual risk factors. We have focused on mental health changes at the cut-off dates only, not the differences in the entire time span. Therefore, we do not rely on the results shown in Tables 2 and 3.

Overall, the coefficients suggest a statistically significant fall in both anxiety and distress scores at the two policy changes dates. The fall in GAD-7 score at the first and second cut-off dates was -0.513 (95%CI: -0.913, -0.112) and -1.148 (95%CI: -1.800, -0.496), respectively. The corresponding figures for IES-R were -2.620 (95%CI: -4.279, -0.961) and -3.449 (95%CI: -5.725, -1.172), respectively. These figures suggest that both anxiety and distress reduced when the lockdown relaxation and the face covering measures were introduced. The reductions in mental health scores were higher when the face covering policy was introduced compared to the start of the lockdown relaxation.

There was no statistically significant reduction in the GAD-7 (0.017, 95%CI: -0.602, 0.673) and IES-R scores (-1.643, 95%CI: -3.914, 0.628) for health workers and other key workers (GAD-7: -0.756, 95%CI: -1.877, 0.365; IES-R: -1.704, 95%CI: -5.115, 1.708) at the first cut-off date. However, for health workers, when face covering was introduced the GAD-7 score reduced significantly, although there was no significant change in their IES-R score. At the second cut-off date, other key workers had a significant reduction in IES-R (-5.458, 95%CI: -9.144, -1.772) but no statistically significant change in GAD-7 score (-1.421, 95%CI: -3.454, 0.613).

Anxiety and distress scores significantly reduced for both females (GAD-7: -0.496, 95%CI: -0.983, -0.010; IES-R: -2.606, 95%CI: -4.445, -0.767) and males (GAD-7: -0.622, 95%CI: -1.653, 0.409; IES-R: 2.461, 95%CI: -5.929, 1.007) at the first cut-off date and also at the second cut-off date (females: GAD-7: -1.013, 95%CI: -1.778, -0.248; IES-R: -3.369, 95%CI: -5.789, -0.948) (males: GAD-7: -1739, 95%CI: -2.993, -0.485; IES-R: -3.112, 95%CI:

-6.985, -0.762). At both dates, the fall in GAD-7 were higher among males compared to females. IES-R shows the opposite picture. Those below 21 years of age showed a statistically significant decline in GAD-7 (-5.482: 95%CI: -9.526, -1.437) at the first cut-off date compared to all other age groups. However, the reductions in mental health scores were not statistically significant in the below 21 years group when the face covering policy was introduced (GAD-7: -0.983, 95%CI: -5.502, 3.536).

People from white ethnic background had a significant reduction in GAD-7 (-0.657, 95%CI: -1.129, -0.185 at the first cut-off date; and -1.243, 95%CI: -1.957, -0.529 at the second cut-off date) and IES-R (-3.044, 95%CI: -4.830, -1.259 at the first cut-off date; -3.567, 95%CI: -5.888, -1.246 at the second cut-off date). There was no statistically significant change in the mental health status of non-white ethic population in the study.

Christians had a statistically significant fall in GAD-7 (-0.652, 95%CI: -1.298, -0.006 at the first cut-off date; -0.928, 95%CI: -1.630, -0.226 at the second cut-off date) and IES-R (-2.679, 95%CI: -4.909, -0.449 at the first cut-off date; -3.354, 95%CI: -6.289, -0.420 at the second cut-off date). At the first cut-off date, non-Christians had a significant decrease only in IES-R (-3.473, 95%CI: -6.483, -0.464). At the second cut-off date, non-Christians had a significant reduction in GAD-7 (-1.298, 95%CI: -2.290, -0.306) and IES-R: (-3.473, 95%CI: -6.483, -0.464).

There were significant reductions in the anxiety and distress scores of people with A-level or below and higher degree at both cut-off points. However, for higher degree holders, the improvements in mental health were seen only in IES-R (-1.955, 95%CI: -3.408, -0.502) at the first cut-off date and GAD-7 at the second cut-off date (-0.876, 95%CI: -1.712, -0.041). The lower educated group had a greater improvement in mental health at both cut-off dates.

People living in rented accommodation did not report improvements in their mental health at the first cut-off date (GAD-7: -0.369, 95%CI: -1.449, 0.712; IES-R: -1.933, 95%CI: -5.935, 2.068), but did report an improvement at the second cut-off date for GAD-7 only (-1.837, 95%CI: -3.056, -0.618). Those living in their own accommodation had statistically significant improvements in both GAD-7 and IES-R at both cut-off dates.

Those who were shielding did not report any improvements in their mental health at the first cut-off date (GAD-7: -0.655, 95%CI: -2.023, 0.713 and IES-R: -3.447, 95%CI: -8.512, 1.619). There was improvement in GAD-7 at the second cut-off date for this group. Those who were not shielding had no improvement in mental health, except for GAD-7 at the first cut-off date (-1.243, 95%CI: -2.295, -0.191).

Those who experienced COVID-19 illness reported an improvement in their mental health status at the first (GAD-7: -0.490, 95%CI: -0.961, -0.018) and second (GAD-7: -0.875, 95%CI: -1.621, -0.129) cut-off dates. Those who did not experience any such problems reported an improvement in their mental health at the second cut-off date only.

People who had previous mental health conditions did not experience statistically significant improvements in their mental health at the first cut-off date (GAD-7: -0.649 95%CI: -1.582, 0.284; IES-R: -2.772, 95%CI: -6.246, 0.702). At the second cut-off date, there was improvement for this group in IES-R (-6.239, 95%CI: -10.192, -2.286), but not in GAD-7. For those with no mental health issues, improvement in GAD-7 was noted at the second cut-off date.

Statistically significant improvement in mental health was seen at the first cut-off date among respondents who drank alcohol 4 or more times in a week (GAD-7: -1.165, 95%CI: -2.178, -0.151; IES-R: -3.784, 95%CI: -7.229, -0.340). At the second cut-off date, those who drank alcohol moderately had statistically significant improvement in the measured mental health indices. Those who were taking drugs did not experience an improvement in their mental health scores at the first (GAD-7: 0.631, 95%CI: -3.023, 4.286; IES-R: -2.827, 95%CI: -12.067, 6.412) or second cut-off dates (GAD-7: -1.470, 95%CI: -6.338, 3.398; IES-R: 5.805, 95%CI: -11.429, 23.039). However, at both cut-off dates, there were significant improvements in the mental health of those who did not take drugs.

Those who reported suicidal thoughts ever in their life showed improvements in their mental health at the first cut-off date (GAD-7: -1.232, 95%CI: -1.983, -0.481; IES-R: -5.938, 95%CI: -8.759, -3.118), but not at the second cut-off date (GAD-7: -1.588, 95%CI: -3.487, 0.310; IES-R: -4.256, 95%CI: -9.486, 0.974). However, those who had no suicidal thoughts had no improvements in their mental health at the first cut-off date (GAD-7: -0.173, 95%CI: -0.599, 0.252; IES-R: -0.941, 95%CI: -2.482, 0.600), but did improve at the second cut-off date (GAD-7: -0.831, 95%CI: -1.343, -0.319; IES-R: -2.520, 95%CI: -4.065, -0.975).

Robustness check

These results would be robust if the local randomization exists around the cut-off (policy changing) dates, meaning that individuals are randomly distributed around the cut-offs. If it can be shown that all control variables (*e.g.*, demographics, pre-existing health conditions, and lifestyles, which are dummy variables) are insignificantly discontinuous at those cut-off dates, it can be said that the local randomization exists around those cut-offs. In other words, insignificant discontinuities in control variables will guarantee that significant discontinuities in mental health scores (GAD-7 and IES-R) happen due only to policy changes (relaxation of lockdown and face-covering), not due to changes in the control variables, which also affect those mental health scores.

Separate OLS regressions of every control dummy following the same RDD specification in equation were run. The outcome variable was just replaced with the control dummy. Every dummy has a base category, for which the dummy variable is not needed; otherwise, there would be a dummy trap. For that reason, when the male dummy is used, for example, the female dummy is not needed, and Supplementary Table 1 does not show results for that reason. The coefficients of the discontinuity dummies for two cut-off dates, with 95%CI, are shown in Supplementary Table 1 in Supplementary material. As both GAD-7 and IES-R had different sizes of samples, two groups of such regressions of control variables were run using two different common samples of GAD-7 and IES-R. Common samples come from the regressions of those mental health scores. Results in Supplementary Table 1 imply that most of the control dummies are insignificantly discontinuous, implying that the main results in Table 4 are mostly robust.

Other biases (caused by unobserved factors', changes or any other policy changes that affect mental health outcomes) can be captured by checking discontinuities in the density of the assignment/trend variable. We found this was statistically insignificant (not shown). There were no other national policy changes at exactly those cut-off dates. From the visual inspection of Figures 2 and 3, there were no clear discontinuities in mental health outcomes at any other dates. If discontinuities in mental health outcomes at the policy changing cutoff dates were random events, there would have been such discontinuities at other dates. This informal falsification test also implies that our results capture mostly causal effects.

Limitations

A key limitation of this study is a high number of missing cases and non-random selection of participants. However, the methodology used in this study mitigates against this limitation by comparing matching cases before and after each policy intervention. Identification tests imply that local randomization exists around the cut-off dates, implying that the findings are robust.

Another limitation is the non-probability sample design and time limited survey which means longitudinal changes were not possible to elicit. Similarly, pre pandemic data was not available, although this was not possible for this survey which was not designed pre pandemic. However, the results from phase one will be compared to phase two of the survey that was conducted from November 20, 2020 to February 2021.

DISCUSSION

This paper examined the association of the lockdown relaxation and the implementation of the face covering policy on the mental health of the general population and sub-groups in the United Kingdom using interrupted time series model. Mental health status was measured using two standardised mental health measures, GAD-7 and IES-R.

This study in the United Kingdom reports a casual association of lockdown on mental health of the participants. The findings compare with similar research carried out in the United Kingdom which showed "minimal" impact of lockdown on the mental health of the general population[1,8,9]. One of the reasons for "mild" anxiety and distress in the United Kingdom during lockdown may be because of several economic and welfare government policies.

This study confirms improvements in anxiety and distress levels following lockdown relaxations. Relaxation of lockdown started on July 4, 2020 in the United Kingdom and showed significant improvements in the population's mental health conditions. However, much greater improvement in anxiety and distress was observed

when face covering in public places was enforced on July 24, 2020. It appears that face covering provided confidence in protection from the virus while visiting friends, public places, clinics, shops and other such places. It may be noted here that when lockdown relaxations were implemented on July 4, 2020, face covering use in the United Kingdom was very limited. Face covering implementation in public places had a significant positive association with mental health on all population sub-groups, suggesting wider benefit of the face covering policy on mental health.

This study identified significantly higher levels of anxiety and distress among people with pre-existing mental health issues, those who were shielding, those who reported suicidal thoughts, drug and alcohol use, and experience of episodes of COVID-19 illness. These population sub-groups benefited by both lockdown relaxation and face covering policy. However, face covering had a greater association with improvement in anxiety and distress than lockdown relaxation.

Higher levels of anxiety and distress among females and younger age groups were noted in this study, which is similar to the emerging global evidence[20]. The findings also compare to other studies that have reported differential impact of COVID-19 Lockdown restrictions on mental health by predisposing health conditions and socio-demographic characteristics. An international study carried out by CARE in 40 countries showed that 27% of women reported an increase in challenges associated with mental illness compared to only 10% of men[20]. A study carried out in Tunisia showed anxiety, depressive symptoms, and stress were found in about 85% of women [21]. Other studies also reported experience of higher mental health problems among females compared to males[6]. A meta-analysis of 206 studies showed minimal differences in the prevalence of mental health issues such as anxiety, depression, and PTSD among healthcare professionals and the public during the pandemic. A new development in this study was that there appears to be higher prevalence of suicidal thoughts/ideation or self-harm (11% *vs* 5.8%) and lower prevalence of wellbeing (28.2% *vs* 52.6%) among the public compared to healthcare professionals which had previously not been reported[22]. Globally there is evidence of domestic violence and more workload for women than men during lockdown[23-26]. There is evidence of lower participation of women in COVID-19 related policy committees[27].

Similar to findings from this study, there is evidence from various studies that the younger age groups had higher levels of mental health problems during lockdown restrictions compared to older age groups[6]. However, older adults have shown lower sleeping quality during the pandemic period compared to the pre-pandemic period[28].

Health workers, particularly frontline staff, played an important role during the pandemic. At the beginning of the pandemic, there is evidence of increased mental health impact on health workers. For example, at the time of COVID-19 in China and Japan, depression, anxiety, insomnia and resilience were higher among frontline health workers than the general population[29,30]. The prevalence of depression, anxiety, and stress has been shown to have remained elevated even after the restrictions were lifted in a study in Malaysia[31]. In this study, anxiety and stress levels of health workers were lower than other key workers. The reason for low levels of anxiety and stress among health workers is currently less understood and a probable reason could be their professional attitude and support from the general public for the important work they do for the country. One can also hypothesise that the health workers learned self-help stress-management and mindfulness that they prescribed to their patients[32]. Studies have also reported increased mental health problems in those who had chronic/psychiatric illnesses, unemployment, student status, and frequent exposure to social media/news concerning COVID-19, compared to their counterparts[6,33]. Living alone during the lockdown, a longer duration of illness, and smoking habits had higher associations with COVID-19 related distress [34]. Detachment, pre-existing mental health problems, fewer coping strategies and childlessness were associated with higher levels of depression and stress[35]. Our study shows similar findings, thereby endorsing the evidence base of the impact of the pandemic.

CONCLUSION

In conclusion, evidence is building on the differential psychological impact of the pandemic, resultant restrictions and policies, based on socio-demographic variables, pre-existing vulnerabilities and health care worker status that will help future planning and policies. Such evidence when used collectively should inform future

planning for pandemics and develop collective and individual physical and mental resilience.

ARTICLE HIGHLIGHTS

Research background

The global pandemic caused by coronavirus disease 2019 has led to wide spread changes in people's day to day lives.

Research motivation

The changes in people's lives and livelihoods due to the global pandemic, associated lockdowns and government guidance is anticipated to have a great impact on people's emotional and social wellbeing.

Research objectives

Positive association of lockdown relaxation and face covering policies on the Mental Health of various population sub-groups is reported.

Research methods

A regression discontinuity design was used to analyse data gathered on people's health and wellbeing during different time periods and restrictions *via* online survey platform.

Research results

In comparison to other key workers and non-key workers during lock down, professional groups and health workers had lower generalised anxiety disorder (GAD-7) scores indicating lower anxiety levels. Similar findings were noted for the impact of events scale-revised (IES-R) scores with health workers, indicating lower levels of distress. During the compulsory face covering phase, there were improvements in mental health scores for all three professional groups assessed by GAD-7 and IES-R. Greater improvements in mental health scores were found among non-key workers than key workers. Gender was associated with different mental health outcomes during the lockdown, with females scoring higher on the GAD-7 and IES-R scales in comparison to males. However, both groups showed a significant improvement in mental health status during the period of face covering, with slightly higher improvements noted in males.

Research conclusions

An impact on people's wellbeing was found, with anxiety and depression levels improving when relaxations in restrictions happened.

Research perspectives

Further investigation into pandemic preparedness for those with pre-existing conditions such as anxiety, depression or obsessive-compulsive disorders and modifying psychological interventions in this population is warranted.

ACKNOWLEDGEMENTS

We would like to thank all the participants who gave their time to complete the survey. We also thank our collaborators–NHS and non-NHS organisations that disseminated the survey.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1366-1386

DOI: 10.5498/wjp.v11.i12.1366

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Autism spectrum disorder and personality disorders: Comorbidity and differential diagnosis

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Author contributions: Rinaldi C wrote the paper and collected and interpreted the data; Attanasio M incorporated changes during the course of review and edited the paper; Valenti M and Mazza M reviewed and critically revised the paper; Keller R conceived, supervised and reviewed the study and finalized the manuscript. All authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interests for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Italy

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

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Abstract

BACKGROUND

Differential diagnosis, comorbidities and overlaps with other psychiatric disorders are common among adults with autism spectrum disorder (ASD), but clinical assessments often omit screening for personality disorders (PD), which are especially common in individuals with high-functioning ASD where there is less need for support.

AIM

To summarize the research findings on PD in adults with ASD and without intellectual disability, focusing on comorbidity and differential diagnosis.

METHODS

PubMed searches were performed using the key words "Asperger's Syndrome", "Autism", "Personality", "Personality disorder" and "comorbidity" in order to identify relevant articles published in English. Grey literature was identified through searching Google Scholar. The literature reviews and reference sections of selected papers were also examined for additional potential studies. The search was restricted to studies published up to April 2020. This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method.

RESULTS

The search found 22 studies carried out on ASD adults without intellectual disability that met the inclusion criteria: 16 evaluated personality profiles or PD in ASD (comorbidity), five compared ASD and PD (differential diagnosis) and one performed both tasks. There were significant differences in the methodological

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

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Received: February 17, 2021
Peer-review started: February 17, 2021
First decision: May 13, 2021
Revised: May 26, 2021
Accepted: November 24, 2021
Article in press: November 24, 2021
Published online: December 19, 2021

P-Reviewer: Li Q, Wei EH
S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

approaches, including the ASD diagnostic instruments and personality measures. Cluster A and cluster C PD are the most frequent co-occurring PD, but overlapping features should be considered. Data on differential diagnosis were only found with cluster A and cluster B PD.

CONCLUSION
ASD in high-functioning adults is associated with a distinct personality profile even if variability exists. Further studies are needed to explore the complex relationship between ASD and PD.

Key Words: Autism spectrum disorder; Asperger's Syndrome; Personality disorder; Adulthood; Comorbidity; Differential diagnosis

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Core Tip: Differential diagnosis, comorbidities and overlaps with other psychiatric disorders are common among adults with autism spectrum disorder (ASD). Findings of most studies support that ASD in high-functioning adults is associated with a distinct personality profile even if variability exists. Cluster A and cluster C personality disorders (PD) are the most frequent co-occurring PD in ASD, but overlapping features should be considered.

Citation: Rinaldi C, Attanasio M, Valenti M, Mazza M, Keller R. Autism spectrum disorder and personality disorders: Comorbidity and differential diagnosis. *World J Psychiatr* 2021; 11(12): 1366-1386
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1366.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1366

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with an early onset and a genetic component. ASD is characterized by deficits in socio-emotional reciprocity, by impaired verbal and non-verbal communication skills, and by an inability to develop and maintain adequate social relationships with peers, and is associated with the presence of repetitive verbal and motor behaviours, restricted patterns of interest, the need for an unchanging (or at least predictable and stable) environment and *hypo- or hypersensitivity* to *sensory* inputs. The onset of clinical symptoms occurs during the early years of life[1].

The severity of ASD symptoms, intellectual functioning, age at diagnosis and psychiatric comorbidity have been shown to account for heterogeneity in clinical presentation, functioning and outcome[2-4].

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition[1], classifies three levels of ASD functioning. Level 1, which requires support, is the best functioning and includes the previous definitions of high-functioning ASD (a term commonly used in clinical practice) and Asperger's syndrome (AS), the closest to neurotypical functioning[1]. ASD level 1 may not have been diagnosed in adulthood and may also have been misdiagnosed as a psychiatric disorder[5,6]. Late-diagnosed individuals show higher levels of co-occurring psychiatric conditions, potentially related to the long-term stress in adaptation to daily life in society[7].

The most common coexisting psychiatric disorders in subjects with ASD include attention deficit hyperactivity disorder (ADHD)[8], obsessive–compulsive disorder[9,10], psychosis[11-13] and mood and anxiety disorders[14-16]. It is possible that adults with ASD level 1 are vulnerable to such disorders[17], in part because of their greater insight into their deficits[18] and greater sensitivity to discrimination[19].

The high frequency of co-occurring disorders and the development of learnt or camouflaging strategies[20] make it difficult to diagnose ASD in adults, especially in women[21,22]. Misdiagnosis, differential diagnoses, comorbidities and overlapping behaviour with other psychiatric diagnoses, as well as personality disorders (PD), should be considered[23]. While these patients are usually screened for the presence of

Axis I disorders, Axis II comorbidities are less often evaluated in this sample of patients[15]. However, in a recent survey Keller *et al*[24] found a PD comorbidity in ASD in 24% of the sample.

PD are enduring and pervasive patterns of inner experience and behaviour that deviate markedly from the expectations of the individual's culture, resulting in distress and impairment[1]. Both PD and ASD are life-long and egosyntonic disorders.

There is a growing interest in exploring the complex relationship between ASD and PD, because a better understanding of this topic may enhance the diagnostic process and also inform targeted interventions.

The purpose of this review is to summarize the research findings on PD in adults with ASD, focusing on comorbidity and differential diagnosis.

MATERIALS AND METHODS

The present review adhered to the standards set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[25]. A systematic review of the literature was performed through PubMed, using combinations of the following search terms: Asperger's Syndrome or/Autism + Personality/Personality disorder or + comorbidity. The search was restricted to studies published up to April 2020. Grey literature was identified through searching Google Scholar. The literature reviews and reference sections of selected papers were also examined for additional potential studies. All records that remained following the removal of duplicates were screened for the inclusion criteria.

Studies were included in this review if they examined PD (as a comorbid or differential diagnosis) in ASD samples. Only studies published in the English language and performed on adults without intellectual disability were selected. In studies for which IQ data were not reported, the participants had to be diagnosed with AS or high-functioning autism (HFA)/ASD level 1. Investigations carried out on non-clinical samples were excluded. Studies evaluating autistic traits in PD patients were also excluded. There were no restrictions made for the geographical region or setting of the study.

RESULTS

Figure 1 shows a PRISMA flow diagram of the systematic research process. The database search yielded a total of 6936 articles. Three additional records were identified through other techniques (ancestry method, grey literature searches and expert consultation). Following the removal of duplicates, 5808 articles remained for screening.

Upon screening of the records, a further 5735 articles were excluded for a variety of reasons, including a focus on different research topics or a failure to satisfy the inclusion criteria. Thus, the full texts of 74 articles were assessed, 22 of which qualified for inclusion.

In order to perform a better analysis, the studies were grouped into two main classes: Those examining personality or PD in ASD adults using categorical and dimensional models (comorbidity); and those comparing ASD with PD on personality traits or psychological functioning (differential diagnosis). In addition, one study[26] performed both tasks.

The characteristics of the studies included in this review are summarized in Table 1.

Seven reviews on psychiatric comorbidity/differential diagnosis of adults with ASD that also referred to PD were found[5,27-32], but only two papers were specifically focused on PD[33,34].

Personality disorders as comorbid diagnosis

Among studies exploring personality features in ASD, only a few assessed PD as a categorical diagnosis using the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)[35,36] or the International Personality Disorder Examination (IPDE)[37] (see Table 2). As autistic traits overlap with aspects of several PD, dimensional measures were preferred to assess personality in adults with ASD.

Structured Clinical Interview for DSM-IV

A study[14] carried out on 117 patients with ASD found that 62% of the sample met

Table 1 Description of the studies included in the systematic review

Ref.	Setting	Aim	Statistical methods	Limitations
Soderstrom *et al* [50], 2002	NeuropsychiatricClinic in Sweden	To study the personality characteristics of adults with AS	One sample *t*-test	Small sample size
Anckarsäter *et al* [47], 2006	Neuropsychiatric Clinic in Sweden	To describe PD in relations to ADHD and ASD symptoms	One sample *t* - test	Non-specific symptoms may be overselected
Ketelaars *et al* [43], 2008	Center of Expertise for Autism in Netherlands	To explore difference between patients with mild ASD and patients without ASD in term of AQ scores and psychiatric comorbidity	X^2 test	Small sample size
Rydén and Bejerot[40], 2008	Psychiatric setting (tertiary unit) in Sweden	To characterize psychiatric patients with ASD in regard to demographical factors, psychiatric comorbidity and personality traits and compare the ASD group with a psychiatric control group; to compare differences of personality traits between females and males in the ASD group.	Fisher exact test; *t*-test; Kruskal-Wallis test	Not ADOS/ADI-R for assessing ASD; A naturalistic study
Hofvander *et al* [14], 2009	Neuropsychiatric Hospital in France NeuropsychiatricClinic in Sweden	To describe the clinical presentation and psychosocial outcome of a group of normal intelligence adults with ASD	X^2 test	Lack of comparison group; Two studies sites; Prevalence of comorbid psychiatric conditions may be overestimated
Sizoo *et al*[49], 2009	Two diagnostic centers specialized for adult patients with developmental disorders in Netherlands	To test whether adults with ASD or ADHD have distinct personality profiles, to assess how personality profiles in these groups differed by SUD status	One sample *t*-test	The clinically based diagnostic procedures; The absence of a psychiatric control group; All participants were diagnosed in adulthood
Geurts and Jansen[44], 2011	Tertiary psychiatric unit from diagnosing ASD in Netherlands	To draw the pathway to a diagnosis for adults referred to ASD assessment	Mann-Whitney *U* tests; Kruskal-Wallis tests; X^2 test	Retrospective chart study; Not standardized clinical interviews for assessing axis I and axis II diagnosis
Kanai *et al*[59], 2011	University Hospital in Japan	To examine the clinical characteristics of adults with AS	Spearman's rank correlation coefficient	Small sample size
Kanai *et al*[67], 2011	University Hospital in Japan	To examine the clinical characteristics of adults with AS	Mann-Whitney *U* test	Small sample size
Lugnegård *et al* [38], 2012	Neuropsychiatric clinics in Sweden	To explore the presence of PD in young adults with AS	X^2 test	Small sample size
Schriber *et al* [55], 2014	Local recruitment by physicians, psychologists, speech and language pathologists, occupational therapists, advocacy groups, regional centers, ASD support groups in United States	To compare self-reports of Big Five personality traits in adults with ASD to those of typically developing adults.	Independent sample *t* -test	Small sample size
Hesselmark *et al* [62], 2015	Tertiary psychiatric unit for diagnosing ASD; a community based facility for ASD; a website for ASD	To test validity and reliability of self-report data using the NEO-PI-R in adults with ASD	Independent sample *t* -test	Small sample size
Strunz *et al*[26], 2015	Department of Psychiatry at a University Hospital in Germany	To identify personality traits in adults with ASD and to differentiate them from patients with NPD, BPD and NCC	MANOVA	Selection bias (BPD and NPD were inpatients, while ASD were outpatients)
Helles *et al*[52], 2016	Neuropsychiatric Centre in Sweden	To examine temperament and character in males who were diagnosed with AS in childhood and followed prospectively over almost two decades	*t*-test; Kruskal-Wallis H testDunn's post hoc test	Only men with AS

Schwartzman *et al*[56], 2016	On line recruitment United States	To assess and compare personality traits of adults with and without elevated ASD traits using; the Five Factor Model of personality	Independent sample *t* -test	Online administration of self-report questionnaires; Sample was not representative of adult population with ASD
Vuijk *et al*[51], 2018	Expertise Centre for Autism in Netherland	To investigated temperament and character dimensions of men with ASD by individual case matching to a comparison group.	*t*-test	Only men with ASD
Ozonoff *et al* [65], 2005	University Child and Adolescent specialized clinic in United States	To explore personality and psychopathology in adult with ASD	Independent sample *t*-test	Small sample size
López-Pérez *et al* [95], 2017	Four different mental health institutions in Spain	To examine use of different interpersonal ER strategies in BPD and AS compared to normative control participants	ANOVA	Self-reports of interpersonal ER; ToM was not assessed
Dudas *et al*[92], 2017	CARD, online responders to a website	To compare ASC, BPD, and comorbid patients in terms of autistic traits, empathy, and systemizing	ANOVA	Diagnosis was based on self-report of patients
Murphy[100], 2006	High security psychiatric care in UK	To compare the ToM performance of three forensic patient groups (AS, Schizophrenia and PD patients)	Kruskal-Wallis H test	No control for the potential influence of medication on cognitive functioning
Stanfield *et al* [87], 2017	Clinical and support services in Scotland; Nonpsychotic people who had previously participated in the EHRS of schizophrenia	To compare Social Cognition in ASD and SPD using functional magnetic resonance imaging (fMRI).	Kruskal- Wallis tests	Small sample size
Booules-Katri *et al*[84], 2019	Patients and relatives of schizophrenia patients attending psychiatric service at a hospital in Spain; Public advertisements	To compare the ToM performance of a group of HFA and SSPD with a matched HC group	*t*-test	SSPD sample consisted of non-clinical individuals

ADHD: Attention deficit hyperactivity disorder; ADI-R: Autism diagnostic interview - revised; ADOS: Autism diagnostic observation schedule-generic; AQ: Autism quotient; AS: Asperger Syndrome; ASC: Autism spectrum condition; ASD: Autism spectrum disorder; BPD: Borderline personality disorder; Er: emotion regulation; HC: Health control; HFA: High-functioning autism; NCC: Non-clinical controls; NEO-PI-R: NEO personality inventory revised; NPD: Narcissistic personality disorder; PD: Personality disorder; SPD: Schizotypal personality disorder; SSPD: Schizotypal-schizoid personality disorder; SUD: Substance use disorder; ToM: Theory of mind.

the criteria for at least one PD: primarily obsessive–compulsive (32%), avoidant (25%) and schizoid PD (21%). Concerning cluster B PD, rates of comorbidity were low, but antisocial disorder was common in the pervasive developmental disorder subgroup. A high number of patients (35%) had more than two PD. The prevalence of PD did not differ between genders, with the exception of schizoid PD, which was significantly more common among women.

Lugnegård *et al*[38] reported that 48% of a sample of 54 young adults with AS fulfilled the criteria for a cluster A or cluster C PD diagnosis. This evidence was in line with Gillberg and Billstedt's review[27] reporting no cluster B PD comorbidity in this sample of patients. It is surprising that paranoid and dependent PD diagnoses were not found. There was a significant difference in PD prevalence between genders: 65% in males versus 32% in females. Patients with AS and a concomitant PD showed more marked autistic features according to the autism spectrum quotient (AQ)[39].

Similarly, no cluster B PD comorbidity was found by Strunz *et al*[26]. In research examining personality pathology in ASD compared to specific PD, 45% of ASD patients met the criteria for an Axis II PD diagnosis. In particular, 36% of ASD patients

Table 2 Summary of included studies exploring comorbid personality disorders diagnosis (according to DSM-IV) in autism spectrum disorder patients

Ref.	Participants	Measures	PD assessment instrument	PD Prevalence (at least one PD)
Ketelaars *et al*[43], 2008	*n* = 15 (4 AS, 10 PDD-NOS, 1 HFA)	AQ, SCAN-2.1	IPDE	> 50%
Rydén and Bejerot[40], 2008	*n* = 84 (5 autistic disorder, 51 AS, 28 PDD-NOS); 37% comorbid ADHD	SCID-I, WAIS III, ASSQ, ASDI, ASRS, MADRS,Y-BOCS, GAF, CGI-S, WRAADDS	SCID-II screen; SPP	> 40%
Hofvander *et al*[14], 2009	*n* = 117 (5 autistic disorder, 62 AS, 50 PDD-NOS)	WAIS-R or WAIS-IIISCID-I, ASDI	SCID-II	62%
Lugnegård *et al*[38], 2012	*n* = 54 (AS)	WAIS-III, DISCOS-11AQ	SCID-II or a structured DSM-IV-based clinical interview	48%
Strunz *et al*[26], 2015	*n* = 59 (49 AS, 10 HFA)	ADOS, ADI-R, MINI, SCID-I, DAPP-BQ,NEO-PI-R	SCID-II	45%
Geurts and Jansen[44], 2011	*n* = 105 (27 autistic disorder, 28 AS, 50 PDD- NOS); 34% of sample with intellectual disability	Former DSM-IV Axis I diagnosis reported	Former DSM-IV Axis II diagnosis reported	15%
Anckarsäter *et al*[47], 2006	*n* = 174 subjects with childhood onset neuropsychiatric disorder (47 ASD, 27 ASD+ADHD, 81 ADHD, 19 other diagnosis)	SCID-I, ASDI, Y-BOCS; ASHFAQ, TCI	SCID- II	75%

ADHD: Attention deficit hyperactivity disorder; ADI-R: Autism Diagnostic interview-revised; ADOS: Autism diagnostic observation schedule-generic; AS: Asperger syndrome; ASD: Autism spectrum disorder; ASDI: Asperger syndrome diagnostic interview; ASHFAQ: Asperger syndrome and high-functioning autism screening questionnaire; ASRS: Adult ADHD self-report scale; ASSQ: Autism spectrum disorder in adults screening questionnaire; ASDI: Asperger syndrome diagnostic interview; AQ: Autism spectrum quotient; CGI-S: Clinical global impression severity of illness; DAPP-BQ: Dimensional assessment of personality pathology; DISCOS-11: Diagnostic interview for social an communication disorder; GAF: Global assessment of functioning; HFA: High-functioning autism; IPDE: International personality disorder examination; MADRS: Montgomery asberg depression rating scale; MINI: Mini international neuropsychiatric interview; NEO-PI-R: Neo personality inventory revised; PDD-NOS: Pervasive developmental disorder not otherwise specified; SCAN-2.1: Schedules for clinical assessment in neuropsychiatry; SCID-I: Structured clinical interview for DSM-IV axis I disorders; SCID-II: Structured clinical interview for DSM-IV personality disorders; SPP: Swedish universities scales of personality; TCI: Temperament and character inventory; Y-BOCS: Yale -brown obsessive compulsive scale; WAIS-R: Wechsler adult intelligence scale-revised; WAIS-III: Wechsler adult intelligence scale-III; WRAADDS: Wender-reimherr adult attention deficit disorder scale.

met the criteria for schizoid PD, 17% for obsessive–compulsive PD and 2% for avoidant and paranoid PD diagnoses.

These findings are in line with those reported by Rydén and Bejerot[40]. They assessed adults with ASD having no intellectual disability using the structured clinical interview for DSM-IV (SCID-II) screen[41] and the Swedish Universities Scales of Personality[42]. Avoidant and schizotypal personality traits were more common in patients with ASD compared to the control group (patients without ASD). Patients with ASD scored higher on detachment and stress susceptibility and had a median of four PD compared to two in the control group. More than 40% of the ASD group reached the cut-off score for avoidant, borderline and obsessive–compulsive PD, more than a third had depressive, schizotypal, schizoid and narcissistic PD and at least 25% reached the cut-off for paranoid and passive-aggressive PD. Females with ASD scored significantly higher than males on borderline and passive-aggressive traits.

In a pilot study on adults with mild ASD, Ketelaars *et al*[43] found partial or complete PD, assessed by the IPDE[37], in more than half of the sample. Schizoid and avoidance were the most frequent PD. There were no significant differences in the pattern of Axis II comorbidity between the ASD and the non-ASD patients.

Instead, in a retrospective chart study[44] on adults screened for ASD, only 15% of ASD patients had a lifetime PD diagnosis. This lower comorbidity is probably due to the fact that one third of the patient group had an intellectual disability. People with autism and an intellectual disability were less likely to receive a diagnosis of PD[45, 46].

In a study on Temperament Character Inventory (TCI) profiles in ASD and ADHD [47], the presence of PD was assessed with the SCID-II in a subgroup of patients with childhood onset of a neuropsychiatric disorder: 75% of the sample met the criteria for at least one PD. Specific PD prevalences are presented in Table 3.

Table 3 Specific personality disorders (Structured clinical interview for DSM-IV axis II diagnosis) prevalence in autism spectrum disorder samples

PD	Lugnegård *et al*[38], 2012	Hofvander *et al*[14], 2009	Anckarsäter *et al*[47], 2006	Strunz *et al*[26], 2015
Paranoid	0%	19%	25.5 % ASD; 25.9% ASD + ADHD	2%
Schizoid	26%	13%	31.9% ASD; 22.2% ASD + ADHD	36%
Schizotypal	2%	21%	23.4% ASD; 11.1% ASD + ADHD	0%
Antisocial	0%	3%	0% ASD; 18.5% ASD + ADHD	0%
Histrionic	0%	0%	0%	0%
Borderline	0%	9%	10.6% ASD; 14.8% ASD + ADHD	0%
Narcissistic	0%	3%	6.4%ASD; 3.7% ASD + ADHD	0%
Avoidant	13%	25%	34% ASD; 11.1% ASD + ADHD	2%
Obsessive-compulsive	19%	32%	42.6% ASD; 29.6% ASD + ADHD	17%
Dependent	0%	5%	8.5% ASD; 22.2% ASD + ADHD	0%

PD: Personality disorders; ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder.

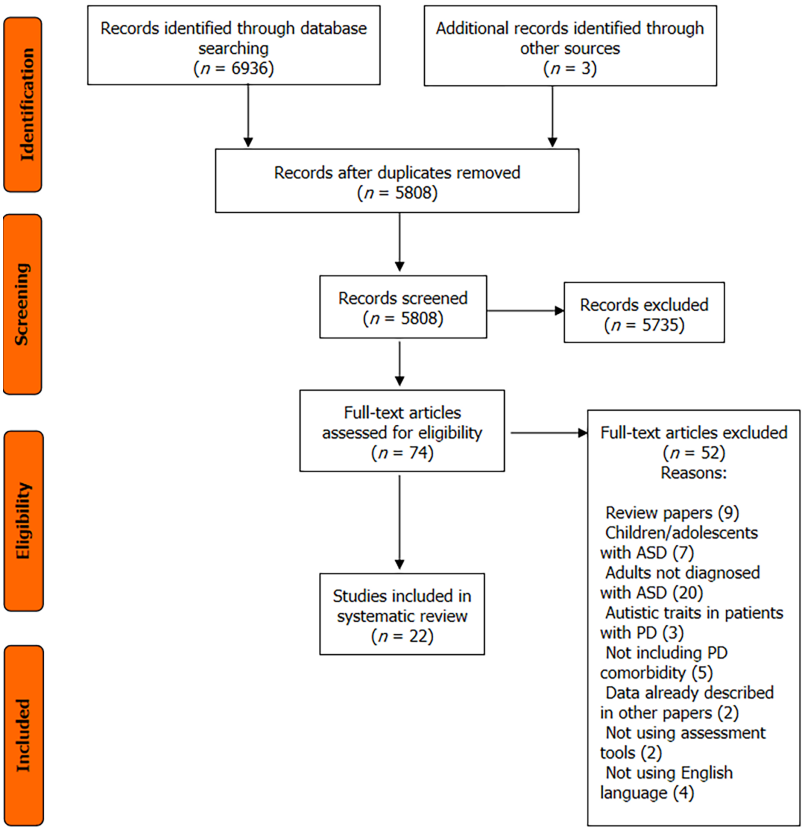


Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram of the systematic research process.

Temperament and character inventory

Studies using the temperament and character inventory (TCI) to evaluate personality in patients with ASD are presented in Table 4[48]. Four TCI studies on adults with ASD[47,49-51] found low scores on the character dimensions of self-directedness and cooperativeness. Moreover, ASD was associated with high harm avoidance, low reward dependence, low novelty seeking and high self-transcendence. The high level of rare answer scores also reflects the oddity and social insensitivity inherent in the self-descriptions of subjects with ASD[50,52]. Cluster A and cluster C PD were more common in patients with ASD assessed with the TCI and confirmed with the SCID-II

Table 4 Summary of studies using temperament character inventory to evaluate personality in adults with autism spectrum disorder

Ref.	Participants	Comparison group	Measures	Personality measures	Results
Anckarsäter *et al*[47], 2006	*n* = 113 (6 autistic disorder, 46 AS, 66 Atypical Autism); 47ASD+ADHD 66 ASD	Age and sex matched group	SCID-I; ASDI; Y-BOCS; ASHFAQ; TCI	TCI; SCID-II	Lower NS, RD, SD, C; Higher HA; Cluster A and Cluster C PD were common
Soderstrom *et al*[50], 2002	*n* = 31 AS	Age and sex matched group	WAIS-III	TCI	Higher HA ST; Lower NS, RD, SD, C
Sizoo *et al*[49], 2009	*n* = 75 (53 without SUD, 8 with past SUD, 14 with current SUD)	*n* = 657 NC	ADI-R; ADOS; DSM-IV criteria checklists; WAIS-III	VTCI	Higher HA, ST; Lower RD, SD, C; Lower NS and RD for ASD without SUD; Higher P for subgroups with current or past SUD
Vuijk *et al*[51], 2018	*n* = 66 (15 ASD, 25 AS, 26 PDD-NOS)	Matched comparison group (age, education, marital status)		TCI	Higher HA, lower NS, RD, SD, C
Helles *et al* [52], 2016	*n* = 40 AS	Within comparison group (no longer ASD/ASD pure/ASD plus)	GAFWAIS-IIIASDI; BDI; ASRS	TCI	Higher RD in no longer ASD; Higher HA, lower NS in ASD pure; Higher HA, lower C, SD in ASD plus

C: Cooperativeness; HA: Harm avoidance; NC: Neurotypical controls; NS: Novelty Seeking; P: Persistence; RD: Reward dependence; SD: Self-directedness; ST: Self-transcendence; SUD: Substance use disorder; SUD: No history of SUD; VTCI: Short version of temperament character inventory.

[47].

In the sample of AS patients included in another TCI study[50], the obsessional type of PD was the most frequent, followed by the passive-dependent, explosive and passive-aggressive types.

The TCI profiles differed somewhat when ASD was combined with a comorbid disorder such as ADHD[47] or substance abuse[49]. When ASD was comorbid with ADHD this was associated with higher levels of novelty seeking, whereas when ASD was comorbid with substance abuse this was associated with a higher degree of persistence and a lower degree of self-directedness compared to ASD patients without the comorbidity.

There was also some evidence indicating an association between temperament and character dimensions and long-term ASD diagnostic stability and psychiatric comorbidity. In a longitudinal cohort study by Helles *et al*[52], the TCI was used to assess 40 males who were diagnosed with AS in childhood and followed prospectively over almost two decades. Three distinct temperament and character profiles emerged. Those no longer meeting the criteria for ASD had high reward dependence. It is also interesting to note that in another study[50] 35.5% of the sample had reward dependence scores above the general population mean, suggesting that a subgroup of individuals with AS desire closer social interaction than they are able to establish. The participants with a stable ASD diagnosis and no current psychiatric comorbidity ('ASD pure group') were characterized by lower novelty seeking and higher harm avoidance compared with normative data; however, compared to the other groups harm avoidance was lower than for the 'ASD plus group' (those with a stable ASD diagnosis and psychiatric comorbidity), which showed elevated harm avoidance and low self-directedness and cooperativeness. In the ASD plus group, comorbidity disorders were depression, anxiety disorder and/or ADHD.

Vuijk *et al*[51] performed a re-analysis of scores on the TCI administered to a sample of 66 ASD men by individual case matching. Compared to the general population, patients with ASD scored significantly higher on the scale for harm avoidance, and lower on novelty seeking, reward dependence, self-directedness, and cooperativeness. These findings confirmed the results emerging from their previous research published in Dutch[53].

Big five personality traits

In Table 5 a summary of studies measuring the Big Five personality traits[54] in ASD patients is presented.

Schriber *et al*[55] investigated personality differences between ASD adults and neurotypical control adults using self-reports of the Big Five personality traits. Individuals with ASD were more neurotic, and less extraverted, agreeable, conscientious and open to experience, than neurotypical controls. The same

Table 5 Summary of studies measuring big five personality traits in adults with autism spectrum disorder

Ref.	Partecipants	Comparison group	Measures	Personality trait measures	Results
Schwartzman *et al*[56], 2016	*n* = 364 adults with elevated ASD traits	*n* = 464 adults with lower ASD traits	RAADS-R	IPIP-NEO-120	Neuroticism was positively correlated with ASD symptomatology; Extraversion, openness to experience, conscientiousness, and agreeableness were negatively correlated with ASD; About 70% of the variance in RAADS-R scores accounted for by the IPIP-NEO-120 facets. A great variability in personality traits emerged in the elevated ASD traits group with four distinct clusters of FFM personality types
Schriber *et al*[55], 2014	*n* = 37 ASD (29% HFA, 57% AS, 14% PDD-NOS)	*n* = 42 NC	WAIS; ADOS G	BFI	Higher Neuroticism Lower Openness to experience, Conscientiousness, Extraversion, Agreeableness
Kanai *et al*[67], 2011	*n* = 64 AS	*n* = 65 NC	AQ; HADS; L-SAS	NEO-FFI	AQ, HADS, and L-SAS were significantly higher in AS than in control. Higher Neuroticism, Lower Extraversion, Agreeableness, Conscientiousness AQ correlated with the subscale scores of HADS and NEO-FFI in AS
Strunz *et al*[26], 2015	*n* = 59 ASD(83% AS, 17% HFA)	*n* = 62 NPD,80 BPD, 106 NC	SCID-I/MINI	NEO-PI-R; DAPP BQ; SCID-II	On the NEO-PI-R: Conscientiousness: NCC = ASD > BPD and NPD Neuroticism: NCC < ASD = NPD < BPD; Extraversion: ASD < BPD, NPD, NCCOpenness for experience: ASD < NCC, BPD, NPDAgreeableness: ASD = BPD and NPD > NCCOn the DAPP-BQ: Inhibitedness: ASD = BPD > NCC and NPD Dissocial Behaviour: NCC = ASD < BPD and NPD; Emotional dysregulation: NCC < ASD = NPD < BPD Compulsivity: ASD > BPD, NPD, NCC
Hesselmark *et al*[62], 2015	*n* = 48 ASD	*n* = 53 NC	MINI	NEOPI-R	Satisfactory internal consistency of the NEOPI-R. Neuroticism correlated with psychiatric comorbidity in ASD group

BFI: Big five inventory; L-SAS: Liebowitz social anxiety scale; HADS: Hospital anxiety and depression scale; IPIP-NEO-120: International personality item pool representation of the NEO-PI-R; NEO-PI-R: Neo personality inventory revised.

personality differences were confirmed when controlling for age, gender and self- and parent reports. The findings indicated that the personality profile distinguished between ASD and neurotypical controls but did not significantly distinguish severity symptoms between individuals with ASD.

In another study, Schwartzman *et al*[56] compared adults with and without ASD using the International Personality Item Pool Representation of the NEO-PI-R (IPIP-NEO-120) as a trait measure. The IPIP-NEO-120, following the full-length version of the NEO[57,58], consists of 24 items per factor and 4 items per facet for a total of 120 items. The Big Five facets accounted for 70% of the variance in autism trait scores measured with the Ritvo Autism Asperger's Diagnostic Scale Revised (RAADS-R)[59]. Neuroticism correlated positively with autism symptom severity, whereas extraversion, openness to experience, agreeableness and conscientiousness correlated negatively with autism symptom severity.

The clinical characteristics of AS adults, including depression, anxiety and personality (NEO Five-Factor Inventory, NEO-FFI)[57], were examined by Kanai *et al*[59]. The AQ[39], Hospital Anxiety and Depression Scale (HADS)[60], Liebowitz Social Anxiety Scale (L-SAS)[61] and neuroticism scores were significantly higher in adults with AS than in controls, whereas the extraversion, agreeableness and conscientiousness scores were significantly lower. The total score of the AQ correlated with the anxiety subscale score of the HADS and the extraversion, openness and conscien-

tiousness subscale scores of the NEO-FFI in adults with AS, but not in the controls.

Strunz *et al*[26] assessed personality traits using the NEO-PI-R[62] and personality pathology using the Dimensional Assessment of Personality Pathology (DAPP-BQ)[63, 64] in four samples of adults: ASD, narcissistic PD, borderline PD and non-clinical controls. Personality traits and personality pathology specific to ASD could be identified: ASD individuals, when compared to non-clinical controls, showed significantly higher scores on the NEO-PI-R neuroticism and DAPP-BQ emotional dysregulation dimensions and lower agreeableness scores; ASD individuals had significantly lower scores on the NEO-PI-R extraversion and openness to experience scales and significantly higher scores on the DAPP-BQ inhibitedness and compulsivity scales, relative to all other groups.

Moreover, individuals with ASD scored significantly higher than all other groups on the NEO-PI-R straightforwardness (frankness in expression) subscale. The results of the comparison with PD will be described later as differential diagnosis features.

Minnesota multiphasic personality inventory

Table 6 shows a summary of studies using other assessment measures to evaluate personality in ASD.

Only one study[65] explored personality in HFA by administering the minnesota multiphasic personality inventory (MMPI-2)[66]. The ASD sample had higher scores on the L (Lie) validity scale, Clinical Scale Depression (D) and Social Introversion (Si), Content Scale Social Discomfort (SOD), Supplementary Scale Repression (R) and Personality Psychopathology Five (PSY-5) Introversion (INTR) scales than a matched sample of college students.

In ASD, sample comorbidity conditions were major depression, anxiety disorder and ADHD. The MMPI-2 profile reflected social isolation, interpersonal difficulties, depressed mood and coping deficits. This study also found medium-sized group differences from the control sample and elevations in 30%-40% of the ASD group on Scale 8 (Schizophrenia). These results could be related to psychotic symptoms but also to social alienation and general maladjustment. A high rate of elevation (30%) on the L scale reflects a desire to present a favourable impression and is quite unusual in this sample of patients.

Eysenck personality questionnaire

Kanai *et al*[67] examined 112 adults with AS using the eysenck personality questionnaire (EPQ)[68] and the Schizotypal Personality Questionnaire (SPQ)[69]. Patients scored higher than controls on the SPQ, higher on the neuroticism and psychoticism scores of the EPQ and lower on the extraversion and lie scores of the EPQ. The SPQ subscale scores (unusual perceptual experiences, odd behaviour and suspiciousness) were correlated with the total scores of the AQ in AS.

Personality disorders as differential diagnosis

In the literature investigating the relationship between PD and ASD, differential diagnosis is less explored than comorbidity. Studies comparing individuals with ASD or PD on different assessment measures are shown in Table 7, and each PD cluster is described in terms of differential diagnosis with ASD.

Cluster A personality disorders

Autism and schizophrenia spectrum disorders are classified separately in the DSM-5, but empirical findings suggest that these two disorders share overlapping features[70-72]. In clinical practice the most common difficulties are in the differential diagnosis of adults with ASD from those suffering from schizoid or schizotypal PD[29,73]. It is suggested that attention should be paid to the developmental history of the person, the prodrome and onset of the condition, its course and the absence of positive symptoms [74].

Social cognition (SC) deficits are points of overlap between ASD and schizophrenia spectrum disorders. SC includes cognitive mechanisms involved in the processing and interpretation of the social world[75-79]. Most studies on this topic directly examined patients with autism and schizophrenia[80-83] rather than schizoid or schizotypal patients. Only two studies meeting the inclusion criteria were found.

Booules-Katri *et al*[84] investigated differences in Theory of Mind (ToM), a main component of SC, which refers to the ability to understand the emotional and mental states of other people[75,78,79,85,86]. They used three advanced ToM tests in 35 patients with HFA, 30 patients with schizotypal-schizoid PD (SSPD) and 36 healthy controls: individuals with HFA showed worse performance and no dissociation

Table 6 Summary of studies using different assessment measures to evaluate personality in adults with autism spectrum disorder

Ref.	Participants	Comparison group	Measures	Personality measures	Results
Ozonoff *et al*[65], 2005	*n* = 20 HFA	24 NC (age, intelligence and gender matched college students)	WAIS-R	MMPI-2	Higher Depression, Social Introversion, Social Discomfort, Repression and PSY-5 scale Introversion
Kanai *et al* [59], 2011	*n* = 55 AS	57 NC	WAIS-R	SPQEPQ	SPQ: AS>NC; SPQ subscale scores (unusual perceptual experiences, odd behaviour, and suspiciousness) were correlated with total scores of the AQ in the AS group; Higher 'Neuroticism' and 'Psychoticism'; Lower 'Extraversion' and 'Lie'

EPQ: Eysenck personality questionnaire; MMPI-2: Minnesota multiphasic personality inventory; SPQ: Schizotypal personality questionnaire.

between affective and cognitive ToM components when compared with the SSPD patients; and the SSPD individuals scored significantly lower on cognitive than affective ToM tasks.

Stanfield *et al*[87] compared SC in ASD and schizotypal PD (SPD) using functional magnetic resonance imaging (fMRI). In the Ekman 60-Faces Test and the social judgement task there were no significant differences between the ASD, the SPD and the comorbid groups on any measure. All groups had similar patterns of impairment in the SC tests and few differences in clinical symptoms, but clear differences were seen between the ASD and SPD groups using fMRI during the social judgement task. Hyperactivation in SPD compared to ASD was found in the amygdala and the cerebellum. The fMRI findings for the comorbid group showed differences compared to the ASD group and similarities with the SPD group. The findings supported the hypo- and hyper-mentalizing theory of ASD and schizophrenia, highlighting the difficulty and importance of considering SPD as a differential diagnosis for ASD.

Cluster B personality disorders

In recent years there has been a growing interest in investigating deficits in SC, given the symptomatic overlap between autistic spectrum conditions and borderline PD (BPD)[88-91].

An investigation[92] into the difference and overlap between ASD and BPD was performed by evaluating autistic traits and empathizing and systemizing abilities in four samples: ASD, BPD, comorbid ASD+BPD and controls.

Similar to BPD, ASD patients scored higher than controls on the AQ[39] and the Systemizing Quotient-Revised (SQ-R)[93] but had lower empathizing abilities measured with the Empathy Quotient (EQ)[94]. The major limitations of this study were that diagnosis was based on the patients' self-reports, and that there was a preponderance of females in the BPD and control samples. The results support the view that some females with BPD have undiagnosed ASD.

In another study[95], 30 BPD, 30 AS and 60 matched control participants were compared on interpersonal emotion regulation strategies. Both patients with AS and those with BPD engaged less than the controls in interpersonal affect improvement. No differences were found for affect worsening. Individuals with AS did not differ in affect improvement and worsening, tending to generally engage less in interpersonal emotion regulation. Instead, individuals with AS reported using less adaptive (attention deployment, cognitive change) and more maladaptive (expressive suppression) interpersonal emotion regulation strategies compared to individuals with BPD and controls.

Differential diagnosis between ASD and narcissistic PD (NPD) may also be difficult. NPD was found to be one of the most prevalent PD in a help-seeking population of adults with suspicion of autism without intellectual disability in whom autism could be excluded[96]. Attwood[97] suggested that individuals with ASD, especially those with superior intellectual abilities, may overcompensate for feelings of inadequacy in social situations by becoming arrogant and egocentric.

Strunz *et al*[26] compared BPD, NPD and ASD on personality traits (NEO-PI-R) and personality pathology (DAPP-BQ), reporting different profiles. Adults with ASD had significantly higher scores on the NEO-PI-R conscientiousness dimension and significantly lower scores on the DAPP-BQ dissocial behaviour dimension than BPD and NPD patients. On the corresponding DAPP-BQ compulsivity scale, adults with ASD had significantly higher scores than all other groups.

Table 7 Studies comparing autism spectrum disorder patients with personality disorders patients on different assessment measures

Ref.	Participants	Comparison group	Measures	Results
Strunz *et al* [26], 2015	59 ASD (83% AS, 17% HFA)	62 NPD, 80 BPD, 106 NC	NEO-PI-R; DAPP BQ; SCID-I/MINI; SCID-II	On the NEO-PI-R: Conscientiousness: NCC = ASD > BPD and NPD; Neuroticism: NCC < ASD = NPD < BPD; Extraversion: ASD < BPD, NPD, NCC; Openness for experience: ASD < NCC, BPD, NPD; Agreeableness: ASD = BPD and NPD > NCC; on the DAPP-BQ; Inhibitedness: ASD = BPD > NCC and NPD; Dissocial Behaviour: NCC = ASD < BPD and NPD; Emotional dysregulation: NCC < ASD = NPD < BPD; Compulsivity: ASD > BPD, NPD, NCC
López-Pérez *et al*[95], 2017	30 AS	30 BPD60 matched NC	SCID-ISCID-IIEmotion regulation of others and self (two scales: extrinsic affect improvement, extrinsic affect worsening)Interpersonal emotion management	Affect improvement: BPD = AS < NNC; Affect worsening: BPD = AS = NNC; Affect improvement > affect worsening in BPD e NCC; Affect improvement = affect worsening in ASD; Adaptive interpersonal strategies (attention deployment, cognitive change) ASD < BPD and NNC; Maladaptive interpersonal strategies (expressive suppression) ASD > BPD and control.
Dudas *et al* [92], 2017	624 ASD	23 BPD; 16 ASD+ BPD; 2081 NC	AQ; EQ; SQR; SCID-II	AQ: NC < BPD = ASC < ASC+BPD; EQ:NC = BPD > ASC = ASC+BPD; SQR NC < BPD = ASC = ASC+BPD
Murphy [100]2006	39 AS; Male forensic patients detained in high security psychiatric care	39 PD (antisocial and/or borderline)39 SC with positive symptoms detained in high security psychiatric care	WAIS-R; ToM measures	IQ PD = AS > SC; AS and SC performed worse on two ToM measures (the Revised Eyes Task and the second order mental representation stories)
Stanfield *et al*[87], 2017	28 ASD	21 SPD; 10 CM; 33 NC	ADOS-G; SCID-II; PANSS; WAISsocial judgment taskEkmann 60 facies task; fRMI task of social judgement	SPD = CM = ASD < controls on social judgment task and Ekman 60-Faces Test; on positive symptoms: ASD < SPD = CM; on negative symptoms ASD = SPD > CM; fRMI: hyperactivation in SPD and CM group compared to ASD was found in the amygdala and the cerebellum
Booules-Katri *et al* [84], 2019	35 HFA	SSPD (n = 30) and a NC (n = 36)	O-LIFE questionnaire; SCID-I; SCID-II; ADI-R; ADOS; WAIS-III; ToM test	HFA showed greater impairment and no dissociation between affective and cognitive ToM components; SSPD scored significantly lower on cognitive than affective ToM test

BPD: Borderline personality disorder; CM: Comorbid group (SPD+ASD); EQ: Empathy quotient; NPD: Narcissistic personality disorder; O-LIFE questionnaire: Short version of the Oxford-Liverpool Inventory of Feelings and Experiences questionnaire; PANSS: Positive and negative syndrome scale; NC: Non clinical control group; SQR: Systemizing quotient revised; SSPD: Schizotypal-schizoid personality disorder; ToM: Theory of mind.

In BPD, higher levels of neuroticism, extraversion and openness for experience but less conscientiousness and the same level of agreeableness were found on the NEO-PI-R scores. The study also found, using the DAPP-BQ, more emotional dysregulation and dissocial behaviour and less inhibition and compulsivity in BPD patients compared with ASD patients. On the three inhibitedness subscales, no differences were reported. Even if the underlying causes social avoidance differed between BPD and ASD (social skill deficit in ASD versus fear of rejection in BPD), ASD individuals scored lower on the NEO-PI-R openness to experience dimension but significantly higher on the ideas (intellectual curiosity) subscale than BPD patients.

In relation to the difference between autism and narcissism, ASD patients' scores on the NEO-PI-R modesty and compliance subscales were comparable to non-clinical control subjects. Moreover, patients with ASD and non-clinical controls had similar scores on the DAPP-BQ narcissism subscale.

With regard to differential diagnosis with antisocial PD, different empathic dysfunctions in psychopathy and autism have been found[98,99]. Only one study[100] compared the ToM performances of forensic AS, schizophrenia and PD patients. In the PD group there were individuals with dissocial PD and/or BPD, diagnosed by expert clinicians. Patients were male and detained in high security psychiatric care. The results suggested that the AS and SC groups performed worse than the PD patients on the revised eyes task[101] and the second-order mental representation stories. The AS and PD groups did not differ on the Wechsler Adult Intelligence Scale full-scale IQ but both scored more highly than the SC group.

Cluster C personality disorders

It is well known that the phenomenology of obsessive–compulsive PD shows similarities to that of ASD[102], so misdiagnosis of ASD as anankastic PD is possible. It is suggested to consider first whether an individual has an underlying autism spectrum condition before diagnosing obsessive-compulsive PD[103]. In ASD, repetitive patterns of behaviour, in particular the pursuit of circumscribed interests, are often associated with pleasure and mastery rather than egodystonicity. Gadelkarim *et al*[104] suggested that in obsessive–compulsive patients the presence of obsessive–compulsive PD should alert one to the possible recognition of ASD.

No studies comparing ASD patients with cluster C PD patients met the inclusion criteria.

DISCUSSION

Examining personality in adults with ASD has only become the focus of research in recent years. The current review provides a literature summary of how personality and PD have been studied in high-functioning adults with ASD, focusing on two clinical issues.

The first issue for clinicians evaluating personality in ASD adult patients is to determine whether personality traits are part of the same autistic phenomenology or rather represent different categorical factors (comorbidity). The findings of studies focused on PD comorbidity suggested that approximately 50% of individuals with ASD fulfilled the diagnostic criteria for at least one PD.

The prevalence of PD comorbidity seemed to vary, increasing in samples of patients with other Axis I disorders, especially ADHD, and decreasing in mixed samples with intellectual disabilities. The most common comorbid PD belong to cluster A or cluster C (schizoid, schizotypal, obsessive–compulsive and avoidance PD). High rates of patients with more than one PD were found using the SCID-II. This suggests the utility of completing an assessment with other instruments to answer the question: 'True comorbidity or overlapping features?'[5]. Phenotypic similarities between high-functioning ASD and both schizoid/schizotypal and obsessive–compulsive PD have been noted, but the available data are sparse, so this could be a diagnostic challenge for clinicians[105,106]. An additional PD to an ASD diagnosis could be considered 'true comorbidity' if it gives relevant information for understanding patient functioning and for developing more specific treatments.

In most of the studies reviewed, the personality of adults with ASD was assessed in order to identify a specific profile differing from that of neurotypical controls. Big Five personality traits and the TCI dimensions are the most commonly used taxonomy for measuring personality in adults with ASD. The findings of these studies support the hypothesis that ASD in adults is associated with a distinct personality profile that is not equivalent to an ASD diagnosis or to a specific PD.

Regarding the Big Five traits, these patients have been shown in all the studies reviewed to be higher in neuroticism and lower in extraversion and agreeableness, and also in most of the studies to be lower in openness to experience and conscientiousness. At the same time, ASD characteristics are statistically independent of the Big Five personality traits in clinical samples.

Adults with ASD have repeatedly been shown to have a distinct temperament and character compared to neurotypical controls. Concerning the TCI dimensions, lower scores on the character dimensions of self-directedness and cooperativeness indicated a possible personality psychopathology[107,108]. Moreover, ASD was associated with high harm avoidance, low reward dependence, low novelty seeking and high self-transcendence. High harm avoidance reflects pessimism and shyness, and also state-dependent anxiety. Low reward dependence indicates impairments in social sensitivity, attachment capacity and adaptability. In individuals with an immature

character structure, high self-transcendence may lead to disregard for the basic realities of human interaction and social responsibilities.

As regards other personality measures, such as the EPQ and MMPI-2, the emerging profile reflected social isolation, interpersonal difficulties and psychotic-like symptoms.

In summary, the overall profile of personality traits and dimensions in ASD puts individuals at risk for other psychiatric disorders and lower functioning, even if variability exists.

Individuals with autism that are not diagnosed in childhood may have a high level of stress in trying to find a lifestyle to survive in a world that is difficult to understand; thus, building their personality with this level of chronic stress could be a trigger for creating a PD. Nevertheless, the neuropsychiatric dysfunctions associated with ASD permit considerable variation in personality. It has been suggested that personality mediates the relationship between autistic symptoms and well-being[109,110]. Exploring personality could provide a more comprehensive picture of adults with ASD, characterizing them through their individual strengths and weaknesses. It could advance the understanding of heterogeneity within patients and help in the development of more specific interventions. Treatment of PD comorbidity in adults with ASD is still in its infancy, but specific programmes have started to be developed [111].

The second critical issue is differentiating ASD patients from PD patients in clinical samples when searching for an ASD diagnosis. High-functioning ASD patients are frequently misdiagnosed with PD, and few studies were found on differential diagnosis between ASD and PD.

SC deficits could be useful for distinguishing ASD from PD, especially borderline and antisocial PD[112]. Gender could cause specific patterns of PD comorbidity and increase the risk of misdiagnosis, especially in women[14,113]; it has been suggested that some women with BPD have undiagnosed ASD.

Concerning the difference between autism and narcissism, individuals with ASD may appear egocentric because of a limited awareness of when it is appropriate to compliment oneself and when it is not. Nevertheless, ASD patients were found to be comparable to non-clinical controls on scales measuring narcissism in the only available investigation on this topic[26].

Differences in ToM abilities between ASD and cluster A PD have also been found, but functional neuroimaging may be better than SC testing for discriminating between autism and schizophrenia spectrum disorders[87].

Findings on differential diagnosis should be replicated and investigations should be extended to compare ASD patients with cluster C PD patients too.

Differential diagnosis should be based on clinical examination and a very careful history investigation of the first years of development, the first social relationships with other children and adolescents, changes of lifestyle during development and clinical symptoms of ASD in the first years of life.

Interviews such as the Autism Diagnostic Interview–Revised (ADI-R)[114] could help the clinician to collect the first symptoms of ASD. Personality assessment could help in confirming the diagnosis, but has to be used carefully by an expert clinician who knows the ASD cognitive style in order to avoid misunderstandings.

The findings of all the studies included in this review were based on self-reporting questionnaires or structured interviews that collected information only from the patients. This raises concerns about how a person with autism can read and understand the complex questions in a self-report test: individuals with autism could have difficulties in understanding the real meaning because of their literal way of reading a text. Nevertheless, studies have supported the validity of self-report in adults with ASD without intellectual disability[55,62].

CONCLUSION

This review provides a summary of the main findings in the literature regarding PD in adults with high-functioning ASD without intellectual disability. The aim of the review is to improve knowledge of the complex relationship between ASD and PD. Among the limitations of this review is the exclusion of studies looking for autistic traits in patients with PD or in non-clinical populations, which may be informative for giving a better understanding of overlapping features, as the question of commonality as opposed to comorbidity is not yet resolved. Furthermore, our research was conducted extensively on PubMed only. Future works should be conducted by

optimizing retrieval strategies and also including studies concerning adolescents. Another area little examined is the role of age in modulating the relationship between PD and ASD[115,116]. Longitudinal research on personality and ASD may clarify whether the relationship between personality and ASD increases in adulthood, as has been suggested[55].

ARTICLE HIGHLIGHTS

Research background

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, as well as restricted, repetitive and stereotyped patterns of behaviour. Individuals with high-functioning ASD are more likely to be diagnosed in adulthood, probably due to the development of learnt or camouflaging strategies that make it much harder to identify the underlying difficulties. Late-diagnosed individuals report higher levels of co-occurring psychiatric disorders or misdiagnosis, because some features of ASD can overlap with symptoms of other psychiatric conditions as well as personality disorders (PD). In recent years there has been a growing interest in exploring the complex relationship between ASD and PD, especially for features that overlap with cluster A and cluster C PD.

Research motivation

Consideration of the relationship between PD and ASD, with a focus on differential diagnosis and comorbidity, can lead to a better understanding of this complex topic and can improve the diagnostic process as well as supporting the creation of targeted interventions.

Research objectives

To summarize the research findings on ASD and PD in adulthood, focusing on comorbidity and differential diagnosis.

Research methods

The guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) were followed in the present review. A comprehensive literature search was performed through PubMed, including only studies published in the English language and performed on adults without intellectual disability. The research included studies published up to April 2020.

Research results

The current review provides a literature summary of how personality and PD have been studied in high-functioning adults with ASD. The findings show that approximately 50% of individuals with ASD fulfilled the diagnostic criteria for at least one PD. The most common comorbid PD belong to cluster A or cluster C (schizoid, schizotypal, obsessive–compulsive and avoidance PD). High-functioning ASD patients are frequently misdiagnosed with PD, but only a few studies have been conducted on differential diagnosis. Furthermore, there were significant differences in methodological approaches, including ASD diagnostic instruments and personality measures.

Research conclusions

ASD in high-functioning adults is associated with a distinct personality profile even if variability exists. Cluster A and cluster C PD are the most frequent co-occurring PD, but overlapping features should be considered. Exploring personality could provide greater understanding of adults with ASD by identifying strengths and weaknesses, and could give relevant information for the development of specific and individual treatments.

Research perspectives

Further studies are needed to explore the relationship between ASD and PD, especially on differential diagnosis. It would be useful to explore the relationship between PD and ASD from a longitudinal perspective, take in account individual's life and development history.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1387-1406

DOI: 10.5498/wjp.v11.i12.1387

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Psychological impact of the COVID-19 pandemic on individuals with serious mental disorders: A systematic review of the literature

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Author contributions: Fleischmann E and Dalkner N contributed equally; Fleischmann E collected the data and wrote the first draft of the paper; Dalkner N supervised the study procedure, edited the paper and gave important intellectual input; Fellendorf F and Reininghaus EZ edited the paper and gave important intellectual input.

Conflict-of-interest statement: The authors do not have any conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Austria

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic is having a great impact on individuals from all over the world, particularly on individuals with mental disorders. Several studies found more pronounced psychiatric symptoms, notably symptoms of depression and anxiety.

AIM

To assess the situation of patients with serious mental illness (SMI: Affective disorders and schizophrenia) regarding their mental health outcome during the pandemic.

METHODS

A systematic search using the databases PubMed and MEDLINE was conducted, employing the key words "COVID-19", "SARS-CoV-2", "psychiatric/mental disorder/illness", "affective/mood disorder", "bipolar disorder", "(major) depression", "schizoaffective disorder", and "schizophrenia". Studies that had been published up until January 9, 2021 were included. Information of studies in languages other than English and German was mostly taken from their English abstracts.

RESULTS

The literature search concluded in the finding of 36 studies containing relevant clinical data. A general impairment of the mental health of individuals with SMI could be detected, particularly in individuals with affective disorders, as compared to those with schizophrenia. Compared to healthy controls, symptoms of anxiety, depression, and stress were more pronounced in individuals with SMI. Relevant factors found that impacted their mental health were age, resilience, and socioeconomic environment, especially the shortage of mental health services, lack of social support, and inadequate information about COVID-19.

CONCLUSION

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

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Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: May 13, 2021
Revised: May 27, 2021
Accepted: November 12, 2021
Article in press: November 12, 2021
Published online: December 19, 2021

P-Reviewer: Chakrabarti S, Wang D
S-Editor: Liu M
L-Editor: A
P-Editor: Liu M

In light of these results, mental health services should be reinforced, notably the use of telemental health services. Furthermore, supplying individuals with SMI with adequate information about the COVID-19 pandemic and increasing their resilience is important. When researching the impact of the COVID-19 pandemic on individuals with SMI, standardization as well as follow-up studies are needed to enable better comparability and understanding.

Key Words: COVID-19 pandemic; Serious mental illness; Affective disorders; Bipolar disorder; Major depressive disorder; Schizophrenia

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Core Tip: A greater deterioration was found in individuals with affective disorders, compared to individuals with schizophrenia. Factors influencing the impact on mental health were age, resilience, and socioeconomic circumstances. Consequently, the strengthening of mental health services, including the use of telemental health services with a focus on strengthening resilience, is necessary. Additionally, psychiatric patients should be supplied with appropriate information about the pandemic. In research, follow-up studies and standardization are required.

Citation: Fleischmann E, Dalkner N, Fellendorf FT, Reininghaus EZ. Psychological impact of the COVID-19 pandemic on individuals with serious mental disorders: A systematic review of the literature. *World J Psychiatr* 2021; 11(12): 1387-1406
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1387.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1387

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), is an infectious airborne disease. Initially detected in Wuhan, China[1], in December 2019, it subsequently spread throughout the world and reached the status of a pandemic on March 11, 2020[2]. In order to stop the propagation of the virus, lockdowns comprising measures of physical distancing, travel restrictions, and closure of public facilities were implemented in numerous countries worldwide[3].

The mental condition of both healthy and mentally ill individuals has been affected by the COVID-19 pandemic and its reverberations: Anxiety, distress[4,5], fear of the disease[5], loneliness[6], post-traumatic stress symptoms[7], and the prevalence of depression, anxiety, and suicidality[4,8,9] have been found to be higher in the general population as a consequence of COVID-19. In particular, the prevalence of depression has increased drastically[5,10,11], affecting up to a quarter of the population[12,13], compared to a prevalence of 6.8%-8.5% before the pandemic[10,14]. This is comparable to previous pandemics: During the SARS epidemic in 2003[15] and the West Africa Ebola virus disease pandemic from 2013 to 2016[16], similar effects were observed. Furthermore, economic growth has been stunted, resulting in a rising percentage of unemployment, and thus adding additional distress[17]. The individual condition during the COVID-19 pandemic might have been influenced by personality, resilience [18,19], coping strategies, and socioeconomic environment[20]. In summary, the pandemic in its entirety has led to restrictions of personal rights, heightened emotional distress, and fear of an uncertain future, and may advance the development of mental health problems[17,21].

Individuals already suffering from psychiatric disorders face additional issues that may influence their mental health: Limited resources for medical and psychotherapeutic treatment[22,23] and misinformation[22] have been an additional strain. Furthermore, an increase in social isolation and negative feelings might lead to a worsening of psychiatric symptoms and even illness exacerbation[24-26]. Literature shows conflicting results concerning the impact of the pandemic on the mental health of individuals with psychiatric disorders. On the one hand, symptoms of different mental disorders have been reported to be significantly higher in the wake of the

pandemic[27-31]. On the other hand, there was little to no change in symptomatology found in other studies[25,32-34], showing that more research in this area of interest is necessary.

Individuals with serious mental illness (SMI), which comprise bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SZ), are an especially vulnerable group due to several risk factors[35], such as severe psychiatric illness episodes, hospitalization[36], a lower level of education[37], and cognitive deficits[38-40]. Furthermore, problems when interacting with healthcare services, for instance difficulties adapting to the clinical environment[41], might lead to a worsening of well-being. Post-traumatic stress symptoms have been on the rise in both individuals with mental illness[42-44] as well as the general population[45,46], thus we focused on these symptoms in the course of our search as well. The need for increased support of this particular group of individuals has been highlighted by numerous mental health researchers[26,41,47].

The impact of COVID-19 on individuals with SMI has already been reviewed in June 2020, emphasizing the vulnerability of individuals with SMI and advocating for an increased focus on support for them[35]. Another review by Zhand and Joober[48] included 47 studies with the final search being completed in July 2020, however, the authors focused mainly on SZ spectrum disorders, not mentioning BD and MDD.

Furthermore, a systematic review by Barber *et al*[49], from June 2020, was found. The search yielded four studies, which found that individuals with SMI might show a decline of mental health due to COVID-19-related governmental measures. Furthermore, they experienced increased psychological distress during the crisis.

In comparison with already existing reviews, the current one focuses on the mental health outcome of individuals with SMI in general, encompassing solely papers providing scientific data and including studies that were published at a later time.

The aim of this review is to further broaden the understanding of these complex disorders and thereby provide insight in how to support individuals with SMI during a global crisis. The following questions will be answered: How are individuals with SMI affected by the pandemic in comparison to healthy controls (HC) and what are the main psychiatric symptoms they are displaying? What are risk and protective factors that influence the severity of psychiatric symptoms and who is particularly vulnerable to these factors? How does symptomatology and frequency of illness episodes change during the course of the pandemic?

MATERIALS AND METHODS

We conducted a review of literature for studies about COVID-19 and its impact on SMI in the databases PubMed and MEDLINE (Medical Literature Analysis and Retrieval System Online). The final search was conducted on January 9, 2021.

Inclusion criteria

The main criterion was whether the studies analyzed samples of adults with pre-existing psychiatric disorders (including BD, MDD, and SZ) regarding the impact of COVID-19 on their mental health. Primary outcome variables were those assessing psychological symptoms related to the pandemic.

The following Medical Subject Headings (MESH) search terms were applied in the database PubMed: "COVID-19" OR "SARS-CoV-2" [Title/Abstract] AND "psychiatric/mental disorder/illness" [Title/Abstract] OR "affective/mood disorder" [Title/Abstract] OR "bipolar disorder" [Title/Abstract] OR "(major) depression" [Title/Abstract] OR "schizoaffective disorder" [Title/Abstract] OR "schizophrenia" [Title/Abstract]. The relevance of the studies was determined by inspecting both the title and abstract of each study and the full text of several studies.

The following MESH search terms were applied in the database MEDLINE: "(covid19 or (covid(w)(2019 or 19)) or (corona(w)virus(w)disease(w)2019 or 19)) and (depression? or schizophren? or ptsd or (post(w)traumatic(w)stress))/ti" AND "(covid19 or (covid(w)(2019 or 19)) or (corona(w)virus(w)disease(w)2019 or 19)) and ((mental? or bipolar? or affectiv? or mood? or schizoaffect?)(w)(disorder? or illness?))/ti".

All languages were considered, with an emphasis on English and German literature. The relevance of the studies was determined by firstly inspecting the title of each study, then the abstract of a considerable portion of studies, and finally the full text of several studies.

Exclusion criteria

Scientific studies that were not accessible on publication sites or did not meet the defined criteria were not included: They were not original articles, did not contain scientific data about a sample of patients with SMI (BD, MDD, or SZ) or were not empirical studies, only reported about a single case, or, if they additionally encompassed other mental disorders, did not explicitly mention SMIs.

RESULTS

The results are displayed in Table 1, which encompasses an overview of the 37 analyzed studies. In summary, the following numbers of studies investigating SMI were found either alone or in combination with other disorders: 19 (SMI in general), 9 (affective disorders), 3 (BD), 16 (MDD), and 6 (SZ). The studies included participants from mainly 19 different countries and areas in North America (Canada, United States), Asia (China, India, Taiwan, Turkey), Australia, and Europe (Austria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Netherlands, Norway, Romania, Spain, United Kingdom). Most of them were conducted in the time period from February to June 2020 during periods of physical distancing, thus evaluating mainly the first response to and short-term consequences of the crisis. One study was conducted in January 2020, and another in August and September 2020. The found studies were very heterogenous in samples and study design. Furthermore, not all trials investigated and defined intervention with comparable targets.

Limitations frequently encountered by scientists were small sample sizes, the inability to draw causal conclusions due to cross-sectional sample design, self-reported mental illness without clinical evaluation due to online surveys, possible selection bias, problems of generalization, and the lack of questionnaires measuring pandemic-related variables with the subsequent need to create questionnaires themselves.

How are individuals with SMI affected by the pandemic in comparison to HC and what are the main psychiatric symptoms they are displaying?

Most individuals with SMI had a positive stance regarding measures for preventing COVID-19[50,51], which was related to marriage and a higher level of education[51]. However, they were on average not as knowledgeable about COVID-19 and measures of prevention as HC[52,53]. This reduced knowledge was associated with a low socioeconomic status, little education, and insufficient social support[52]. A higher belief in self-obtained COVID-19 information was related to both more[54,55] and less [50] fear of the disease.

Compared with HC, individuals with SMI showed both more weight gain and frequent changes of sleep patterns[56], however, duration of sleep was found to remain stable over time[57]. An increase in the number of substances used was detected[49,52]. On average, individuals with SMI had fewer social contacts and did not go grocery shopping as often as before the pandemic[58].

Individuals with SMI experienced more symptoms of depression, anxiety[56,59,60], and stress[58-62], partly due to loneliness and isolation[63]. Additional symptoms were elevated feelings of paranoia[59] and isolation[64], self-harm, and suicidal ideation[65]. Fatigue was more prominent in those with a lower quality of life, which was related to severe depressive symptoms, insomnia, and pain[66]. While the majority of subjects with SMI reported to not be worried to get infected[52], they were on average more worried and fearful of contracting COVID-19[58] and made less use of coping strategies than HC[56]. Individuals with SMI were generally more concerned about their financial situation than their own health, although this was found in a study conducted in August and September 2020 and not at the beginning of the pandemic[63].

Individuals with affective disorders displayed both more voluntary self-isolation as well as stress related to it than in HC[67]. Among different disorders, levels of both perceived stress and related somatic complaints, as well as the latter's negative correlation with Clinical Global Impression (CGI), were highest in affective disorders [68]. Psychosocial distress was related to somatization, heightened alertness, psychic anxiety, and bad mood[69]. Other psychiatric manifestations included more symptoms of PTSD in patients with affective disorders than in HC[67], elevated feelings of vulnerability[63], and sleeping problems[61]. Fear about consequences on health[8] and socioeconomic status[67] was heightened in individuals with affective disorders as compared to HC, particularly in younger persons[69].

Table 1 Results of the database search concerning the mental health outcomes of individuals with serious mental illness

Ref.	Country or area, time	Psychiatric disorders	Methods; relevant questionnaires and COVID-19-related variables	Results	Limitations
Asmundson *et al*[67]	Canada and United States, March 21–April 1, 2020 (during the lockdown)	Affective disorders (BD and MDD) and anxiety-related disorders	Cross-sectional case-control online survey of 700 individuals with anxiety-related disorders, 368 individuals with affective disorders and 500 HC; PHQ-4, CSS, self-constructed questionnaires to measure self-isolation distress and coping strategies	Individuals with anxiety-related disorders experienced more COVID-19-related stress, fear, and PTSD symptoms than individuals with affective disorders and HC. Individuals with affective disorders had more PTSD symptoms and fear of socioeconomic consequences than HC. Patients with both BD and MDD exhibited more voluntary self-isolation and stress related to it. Individuals with psychiatric disorders and HC did not differ in the perceived effectiveness of their coping behaviour.	Self-report and not clinical evaluation of mental health, data about comorbidities was not gathered
Burrai *et al*[76]	Italy, April–May, 2020 (during the lockdown)	SZ and other psychotic disorders	Cross-sectional online survey of 77 patients with psychotic disorders and 100 HC; DASS-21, BRCS, COVID-19: Risk Perception (2 items based on Cho and Lee, 2015, and Liao, 2014), self-constructed questionnaire measuring worry	Patients with psychotic disorders were less stressed, more anxious, more worried about the current situation, and perceived the risk of being infected with COVID-19 as higher than HC. Participants with psychotic disorders living in communal residencies were supported by both their cohabitants and mental health professionals, remained adherent to their medication treatment, and possessed knowledge about the consequences of COVID-19.	Significant group differences in gender and education level, geographical limitations, observational design does not allow the determination of causality
Carmassi *et al*[42]	Italy, April 1-30, 2020(during the lockdown)	BD	Telepsychiatry-based cross-sectional clinical interviews and self-reports per e-mail of 100 patients with BD regarding post-traumatic stress symptoms (PTSS); IES-r, GAD-7, HAMD, YMRS	Acute PTSS were experienced by 17% of participants, which was related to COVID-19-related work/financial difficulties as well as anxiety, reported by 26% of participants. Acute symptoms of mania seemed to be protective. Furthermore, 17% of participants reported depressive symptoms.	Small sample size, self-report instruments were less accurate than an assessment by a clinician, not all COVID-19-related stress factors were considered, there was no control group
Chang *et al*[54]	Taiwan, March 23– April 23, 2020 (during the lockdown)	SMI and other disorders	Cross-sectional survey of 400 individuals with mental illness (242 with SZ, 67 with BD, 28 with MDD, and 63 with others); DASS-21, FCV-19S, BCIS, PCIBS	Participants who believed more strongly in the obtained COVID-19 information from newspapers, television, and online sources were more fearful of the disease. A higher level of fear was associated with more symptoms of depression, anxiety, stress, and less frequent behaviour concerning prevention.	Newly constructed questionnaires by using simple measures (BCIS, PCIBS), lack of examination of test-retest reliability (BCIS, SCIBS, FCV-19S) self-reported data, cross-sectional design does not allow the determination of causality
Chang *et al*[55]	Taiwan, March 23– June 30, 2020 (during the lockdown)	SMI, anxiety disorder, and substance use disorder	Cross-sectional survey of 414 patients with psychiatric disorders (197 with SZ, 141 with substance use disorder, 35 with BD, 34 with MDD, and 7 with anxiety disorder); DASS-21, SSS-S, FCV-19S, BCIS, PCIBS	Preventive behaviours recommended by the World Health Organisation could be explained by both COVID-19-related fear and trust in sources of information concerning this disease in individuals with SMI. COVID-19-related fear could be explained by trust in sources of information and self-stigma.	Cross-sectional design does not allow the determination of causality, self-report, bias (common variance, recall, social desirability), stable conditions do not allow generalizability, geographic limitations
Chen *et al*[74]	Taiwan, January–May, 2020 (during the lockdown)	MDD	Long-term follow-up study (structured interviews, at least three follow-ups over a period of three years) of a cohort of 116 patients with treatment-resistant MDD; structured interview about COVID-19-related changes and impact on participants' lives (physical, psychological, and social)	Patients with depression had confidence in the COVID-19-related prevention strategies of the government. They felt distressed about pandemic-related news reports. Patients with MDD have been found to be at a higher risk for suicidality, although the pandemic had a positive impact on some patients as well.	Time limit on interviews and therefore not sufficient collection of variables

Costa *et al*[64]	United States, last week of March 2020 (during the lockdown)	SMI, anxiety disorder, PTSD, OCD, borderline personality disorder, and other disorders	Cross-sectional online survey of 193 individuals with psychiatric disorder (162 with anxiety disorder, 103 with MDD, 78 with BD, 77 with PTSD, 25 with OCD, 24 with BPD, 3 with SZ, and 29 with other disorders; COVID-19-related variables: Self-constructed questionnaires to measure fear, concerns, and social situation	Most of the participants had concerns about their illness and the pandemic. Notably, they were concerned about COVID-19-related service disruption. especially individuals with MDD, who feared a shortage of medication. The diagnosis of MDD was associated with the fear of getting sick. Not coping well was related to feeling socially isolated and worry about not receiving mental health care as well as experience worse psychiatric symptoms. Staying in touch with others by using social media and text messages were seemingly the best communication methods for individuals with coping difficulties related to COVID-19.	Self-constructed questionnaires, self-reported mental illness
Di Nicola *et al*[73]	Italy, April 27-29, 2020 (directly after seven weeks of strict lockdown)	Affective disorders (BD and MDD)	Cross-sectional online survey of 59 remitted patients with MDD and 53 euthymic individuals with BD; K10, medical records, COVID-19-related variables: Lockdown conditions (living alone, changes in work routines, and working on the frontline)	In the sample, 25.9% of subjects experienced no likelihood of distress, 31.2% experienced mild and 42.9% moderate-to-severe likelihood of distress. Severe distress was predicted by low vitamin D levels and MDD diagnosis. Higher levels of distress were more frequently found in individuals who had a longer duration of psychiatric illness, were living by themselves during the lockdown, and had the habit of smoking.	Lack of longitudinal follow-up, self-constructed questionnaires, not all confounding variables for the relation between vitamin D levels and distress were included
Franchini *et al*[69]	Italy, March 9– April 9, 2020 (during the lockdown)	Affective disorders (BD and MDD)	Telephone-based, non-standardized survey of 101 euthymic patients with affective disorders; self-constructed questionnaires measuring emotional stressors and unpleasant lockdown experiences	The most frequently reported stress factor was frustration, which was significantly associated with unemployment, affecting two third of participants. Somatization, heightened alertness, psychic anxiety, and bad mood were related to unemployment as well. Associations between young age and anxiety, increased alertness, and monetary concerns could be found. The participants were satisfied with both the received supplies and information about the pandemic.	Non-standardized survey and therefore problems with generalization
Frank *et al*[61]	Germany, 2nd, and 3rd week of March 2020 (during the lockdown)	SMI, addictive disorders, and others	Cross-sectional, standardized interviews with 196 individuals with mental illness (121 with AD, 41 with SZ, 21 with addictive disorder, and 13 with others); CGI	More than half of participants were feeling more distressed than before the pandemic. Among individuals with affective disorders, 25% had sleeping problems.	Not mentioned
González-Blanco *et al*[62]	Spain, March 19-26, 2020 (during the lockdown, 5 d after the beginning)	SMI: Severe mental disorder (SMD: SZ and BD), and common mental disorder (CMD: MDD and anxiety)	Cross-sectional online survey of 125 individuals with SMD (65 with BD and 60 with psychotic disorders), 250 with CMD (125 with depression and 125 with anxiety), and 250 HC; DASS-21, IES, lifestyle variables	Individuals with SMD reported higher levels of anxiety, depression, and stress than HC, but lower levels than individuals with CMD. After confounding variables were controlled, HC had less anxiety than individuals with SMD with no other differences in psychological factors. In individuals with SMD, anxiety was related to being single, suffering from COVID-19 symptoms, and increased stress levels. Many individuals with SMD (87.2%) could relish free time, however the percentage of HC who could, was higher (94%).	Selection bias and limited representativeness through selective access to digital resources, self-reported diagnoses and psychiatric symptoms, binary scales instead of Likert-type scales to assess behaviour
Hamm *et al*[77]	United States, April 1-23, 2020 (during the lockdown)	MDD	Semi-structured qualitative interviews with 73 older adults (age > 60) with MDD, comparison with pre-pandemic data; PHQ-9, PROMIS anxiety scale	Patients with MDD had a lower quality of life during the pandemic than before, but did not differ in depression, anxiety, and suicidal ideation symptoms. They were resilient and mostly socially connected, worried about both contracting the virus and their mental health, and were not satisfied with governmental measures.	Patients participating may have been too distressed to do so: thus, the survey did not include MDD patients with severe symptoms, distorting results; sample was not ethnically diverse
Hao *et al*[72]	China, February 19-22, 2020 (during the	MDD and anxiety disorder	Cross-sectional online survey of 67 psychiatric patients (45 with mixed anxiety and depression,	Psychiatric patients showed more symptoms of depression, anxiety, stress, PTSD, and insomnia than HC. Additionally,	Generalisation not possible, no biological samples were obtained, low

	lockdown)		19 with other anxiety disorders, and 12 with MDD) and 109 HC; IES-R, DASS-21, ISI	they had more concerns about their physical health and higher levels of anger, impulsivity, and suicidal ideation than HC. The diagnostic criteria for PTSD were possibly fulfilled by more than 30% of participants with mental illness. More than 25% of them had moderate to severe insomnia.	response rate due to online recruitment, geographical limitation, cross-sectional study
Hölzle *et al*[68]	Germany, middle of May 2020 (during the lockdown with loosened restrictions)	SMI, psychotropic dependence, and other disorders	Cross-sectional assessment of 139 psychiatric inpatients (89 with affective disorders, 26 with SZ, 17 with psychotropic substance abuse, and 7 others); CGI, PSS, SRS	The disorders lead to differences in the CGI-score (M = 4.9, SD = 1.0), however, women had higher scores than men. Individuals with AD had the highest levels of both perceived stress and related somatic complaints. Higher CGI-scores were not associated with stress, but with stress-related somatic problems. These correlations were especially high in individuals with AD, and non-existent in individuals with SZ.	Not mentioned
Iasevoli *et al*[59]	Italy, April 13-17, 2020 (during the lockdown, one month after the beginning)	SMI	Telephone-based cross-sectional case-control study of 205 patients with SMI, 51 first-degree relatives, and 205 HC; PSS, GAD-7, PHQ-9, SPEQ	Individuals with SMI were of lower economic status and had more concordant diseases than HC. They experienced more symptoms of anxiety, depression, stress, and paranoia than HC. COVID-19-related stress was an important predictor for anxiety. Comorbidities had an independent influence on anxiety, depression, and stress. Caregivers showed more depressive symptoms than HC.	Not mentioned
Korsnes *et al*[50]	Norway, March–June, 2020 (during and after the lockdown)	SMI, anxiety, and other disorders	Cross-sectional online survey of 19 older (age > 65) psychiatric outpatients (15 with MDD, 2 with cognitive deficit/dementia, 1 with anxiety, and 3 with other diagnoses), 14 inpatients (12 with MDD, 6 with anxiety, 2 with BD, 2 with psychosis, and 1 with another diagnosis), and 46 employees working with them; COVID-19-related variables: Self-constructed questions about fear, prevention measures, risk, and consequences	The majority of patients approved of the strict prevention measures, were not afraid of being infected with COVID-19, and did not think that they would die in case of an infection. Psychiatric patients were generally less concerned about the repercussions of COVID-19 on their health than healthcare employees. Few were very worried, did not welcome the governmental measures, thought the infection risk to be increased the clinic, and/or saw a negative impact on their daily life.	Small sample size, generalisation not possible, self-constructed questionnaires, different times of response (similar measures, but different medial climate)
Liu X. *et al*[82]	China, January 30-February 21, 2020 (during the lockdown)	SZ	Retrospective double centre study of hospitalized SZ patients: 21 suspected to have COVID-19 (11 confirmed), and 30 without suspected COVID-19 infection; PANSS, PSS, HAMA, HAMD, PSQI, COVID-19-related variables: Treatment, symptoms	Schizophrenic patients with suspected COVID-19 had higher levels of stress, depression, and anxiety, and a worse quality of sleep, even after the adjustment for the use of benzodiazepines	Retrospective study: Longitudinal studies and follow-up are needed, assessments for the groups were performed by different doctors
Liu *et al*[70]	United States, April 13–May 19, 2020 (during and after the lockdown)	MDD, anxiety disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, insomnia, and others	Cross-sectional online survey of 898 young adults: 44.6% with mental illness: 38.2% with treatment and 6.2% without treatment (31.7% with depression, 29.0% with anxiety, 8.0% with PTSD, 6.9% with ADHD, 6.7% with insomnia, and 17.7% with others), 23.4% with a suspected mental illness, and 32.2% HC; PHQ-8, GAD-7, PCL-C, MOS-SS, HRQoL, COVID-19-related variables: Self-constructed questionnaires to measure worry and grief	Individuals with a diagnosed (treated or untreated) or suspected psychiatric illness were more likely to have symptoms of depression, anxiety, and PTSD than HC. Individuals who were diagnosed with or suspected to have a psychiatric illness experienced more worries connected to COVID-19, more sleeping problems, and a lower health-related quality of life.	No generalizability due to sample from possible COVID-19 "hotspots", variability in circumstances concerning the time of receiving treatment and/or diagnosis, no diagnosis in suspected cases, no information about treatment and adherence to it, no baseline data for comparison
Ma *et al*[81]	China, January 10–April 30, 2020(before, during, and after the lockdown)	SZ	Case-control assessment of 30 SZ inpatients who were isolated for 14 d and 30 who were not, with a longitudinal comparison of isolated patients	The isolation group experienced more stress, anxiety, and depression than the non-isolation group. After isolation, patients with SZ exhibited higher levels of stress and C-reactive	Small sample size, short observation period, several inflammatory markers were not sufficiently researched with

			before and after isolation; CPSS, PANSS, HAMD, HAMA, PSQI	protein and had a lower quality of sleep.	regard to their impact on social isolation and their correlation with the mental health
Matei *et al*[53]	Romania, March 16–May 14, 2020 (during the lockdown)	SMI and severe AUD	Cross-sectional survey of 115 male psychiatric inpatients (65 with SMI and 50 with severe AUD) and 57 HC; self-constructed questionnaires to measure general knowledge about COVID-19, prevention, and the ability to identify false statements about COVID-19	Patients with SMI were less informed about general knowledge as well as prevention of COVID-19 than HC. Additionally, they were less able to single out false information about COVID-19. Apart from patients with severe AUD being as informed about prevention measures as HC and therefore more informed than patients with SMI, there was no difference between these two groups.	Small sample size, all-male sample, potential selection bias due to the method of selecting HC from residential areas and shopping centres, not representative of all psychiatric illnesses
Muruganandam *et al*[52]	India, at the end of April 2020 (during the lockdown, one month after the beginning)	SMI	Telephone-based cross-sectional survey of 132 patients with SMI and their caregivers; self-constructed interview about COVID-19: Knowledge, perceived social support and aggression, psychiatric symptoms, somatic status	Among the participants, 8.3% did not know about the current pandemic and 75% were neither worried about being infected nor knowledgeable about the symptoms. Additionally, 66% possessed little knowledge about prevention and 20% did not know about the way of transmission. A lack of knowledge was associated with low socioeconomic status, little education, and meager social support. A third exhibited symptoms indicative of a recurrence of their illness.	Small sample size, lack of longitudinal follow-up, lack of healthy control group, self-constructed interview, assessment was not structured, dependence on caregivers' reports on patients' situations
Mutlu and Anıl Yağcıoğlu[36]	Turkey, March 23–April 13, 2020 (before and during the lockdown)	SMI	Telephone-based cross-sectional interviews of 155 individuals with SMI (131 with SZ and 24 with BD) and retrospective data analysis; collection of data about clinical characteristics, medication adherence, and relapse	The total relapse rate in the first trimester of the pandemic was 11% (n = 15 with SZ, n = 2 with BD), with the most frequently related influence being the interruption of antipsychotic medication (59%). However, the relapse rate did not differ from the rate in 2019. Individuals suffering from a relapse had been hospitalized at a more recent date than the individuals who remained stable. Very few patients (n = 2) attempted suicide or had suicidal thoughts during the pandemic.	Not mentioned
Orhan *et al*[77]	Netherlands, January 1, 2018– December 31, 2018 and April 2020 (during the lockdown)	BD	Baseline interviews and cross-sectional survey of 81 older (age ≥ 50) patients with BD; YMRS, CES-D, BAI, SPS, LS, PMS, UC, NEO-FFI, COVID-19-related variables: Fear, mental health impact, positive coping (see Pan *et al*, 2020)	Older patients with BD experienced less psychiatric symptoms during the pandemic compared to the baseline. Loneliness, not having children, passive coping style, low mastery, and neuroticism were associated with more psychiatric symptoms.	Large interval between the collection of baseline data and the interviews during COVID-19 pandemic, only short-time impact, relatively small sample
Pan *et al*[25]	Netherlands, 2006–2016 and April 1–May 13, 2020 (during and after the lockdown)	MDD, anxiety disorder, OCD	Three longitudinal studies with several follow-ups and a cross-sectional online survey of 1181 individuals with psychiatric disorders (1051 with MDD or anxiety and 130 with OCD) and 336 HC during the pandemic; QIDS, BAI, PSWQ, DJGLS	Participants with psychiatric disorders had higher symptoms of depression, anxiety, worry, and loneliness than HC. This was the case before as well as during the pandemic, however, the severity of symptomatology did not increase over time, even showing a slight decrease during the lockdown. In comparison, HC experienced a greater decrease of their mental health than individuals with mental illness.	Different modes of collecting data during face-to-face interviews compared to online surveys during the pandemic, low response rate, no standardised assessment for mental disorders, symptom severity was measured by number of diseases
Pellegrina *et al*[71]	France, during the first wave of the pandemic (during the lockdown)	MDD and anxiety disorder	Retrospective survey of 85 individuals with MDD or anxiety disorder; STAY-YA, Beck BDI-II, COVID-19-related variables: Perception, psychological resources, life conditions	Some participants experienced a worsening of their mood during the lockdown. More pronounced symptoms of both anxiety and depression, sleep disorders and addiction could be found.	Retrospective study: Longitudinal studies and follow-up are needed,
Pinkham *et al*[57]	United States, December 4, 2018–now (still ongoing) and April 3–June 4, 2020 (during and after the lockdown)	SMI	Baseline interviews, online surveys administered three times a day during a 10- or 30-d period before pandemic EMA, and ID-5 (psychosis module), PANa telephone-based cross-sectional survey during the pandemic of 148 patients with	Both affective and psychotic symptoms as well as the duration of sleep remained stable over time. An increase in the number of substances used and psychological well-being was reported, the latter of which was related to female gender and more time spent with other people. The two disorders did not differ in	Data was collected early; longer longitudinal studies should be conducted

			SMI (92 with SZ or schizoaffective disorder and 56 with affective disorder); baseline: MINI, SCSS, YMRS, MADRS, SUMD; EMA: Questionnaires about social life, mood, psychiatric symptoms, substance use well-being, and sleep; phone survey was a combination of baseline and EMA	patterns concerning stability or change.	
Pogany *et al*[63]	Hungary, August 1–September 15, 2020 (after the lockdown)	SMI, anxiety disorder, personality disorder, and others	Retrospective survey of 438 psychiatric patients (39.4% with SZ, 34.6% with affective disorder, 25.0% with anxiety disorder, 0.9% with personality disorder, and 2.7% with others); COVID-19-related variables: "Problem Evaluation Scale" to measure fear, isolation, and healthcare	A third of psychiatric patients felt a worsening of their condition during the time of governmental physical distancing measures, with 12% of them not believing it was related to these measures. Half of patients were feeling distressed because of loneliness and isolation, notably more woman than men. The percentage of individuals with psychiatric disorders who were concerned about their financial situation was higher that the percentage of those who were concerned about own health. Younger patients (age < 50 yr) experienced on average worsened health, were feeling more fearful, and had more difficulties adapting than older patients. In comparison to patients with psychotic disorders, patients with affective disorders were feeling more vulnerable. Patients with SZ had the least problems with a lack of information about COVID-19.	Not mentioned
Quittkat *et al*[58]	Germany, April 2-May 6, 2020(during the lockdown)	MDD, SZ, SP, OCD, GAD, SAD, IA, ED, panic disorder and PA, and BDD	Cross-sectional online survey and retrospective data assessment of 1207 individuals with psychiatric disorders (586 with depression, 135 with GAD, 86 with SAD, 83 with PA, 62 with ED, 47 with OCD, 30 with IA, 16 with BDD, 6 with SP, and 135 others) and 1026 HC; BDSI, CAHSA, DASS-21 (depression subscale), EDE-Q – 2nd ed., PHQ (Panic Model and Stress Subscale), PSWQ-d, SIAS, SPhS, WI, Y-BOCS	All participants had on average fewer social contacts and did not go grocery shopping as often as before the pandemic. All individuals reported augmented levels of psychosocial stress, worried more about COVID-19, and were more fearful of contracting this illness than HC. Among individuals with depression, a quarter perceived an improvement, whereas 57.51% experienced a decrease of their mental health and 45.9% felt the need for more therapeutic support. Individuals with SZ reported mostly no or only slight changes in their mental health and did not find further therapeutic support to be necessary.	Small sample sizes of some groups, retrospective data assessment, self-identification of mental disorders, individuals with mental illness and HC were not matched, possible gender bias, selection bias through method of recruitment, online assessment
Riblet *et al*[78]	United States, October 2019–March 2020 and April 23–May 4 (before and during the lockdown)	SMI	Longitudinal interviews of 11 veterans with SMI (5 with MDD, 5 with BD, and 1 with psychotic disorder), with three in-person interviews conducted before the stay-at-home order (baseline, 1- and 3-mo follow-up) and one telephone-based interview during the lockdown; baseline: MINI; later additions: Hopelessness, social connections, treatment engagement, and suicidal ideation	There were no relevant changes concerning psychiatric symptoms during the pandemic compared to before. Few participants, who were significantly older (M = 71.7 yr) experienced an increase in symptomatology.	Small sample size, geographical limitation: low infection rate in Northern New England, participants consisted solely of veterans with possibly easier treatment access, participants had been hospitalized because of their illness, no long-term follow-up
Rohde *et al*[60]	Denmark, February 1–March 23, 2020 (before and during the lockdown)	SMI, stress-related and adjustment disorders, personality disorders, autism, ED, hyperkinetic disorder, and others	Analysis of clinical notes of 14561 psychiatric inpatients, with 918 of them being further analyzed (198 with SZ, 130 with MDD, 68 with BD, and 522 others); screening of clinical notes for COVID-19-related psychiatric symptoms	The final number of patients with notes describing pandemic-related psychopathology was 918, with two thirds of them being female. Most notes contained symptoms related to logistical problems. The most common symptoms were anxiety (n = 539), stress (n = 174), delusions (n = 149), depression (n = 146), suicidality (n = 102), and obsessive-compulsive symptoms (n = 85).	Lack of systematic assessment for COVID-19-related psychopathology
Solé *et al*[56]	Spain, May 14–June 8, 2020 (during the lockdown)	SMI (SZ or BD and MDD and/or anxiety)	Cross-sectional online survey of 206 individuals with psychiatric illness (148 with BD or SZ and 50 with MDD or anxiety) and 413 HC; self-	In comparison to HC, individuals with psychiatric disorders reported less use of coping strategies, such as having a routine, social interactions, and a healthy lifestyle. Furthermore, they	Lack of generalizability, self-reported mental illness, different restrictions at different times when conducting the

			constructed questionnaires for psychological distress (inspired by GAD-7 and PHQ-9), trauma experiences (inspired by EGS-R), psychotic-like experiences (adapted from CAPE-42), resilience (derived from BRS and RS-14), affective temperament (inspired by TEMPS-A), perceived family environment (inspired by FES), cognitive reserve (based on CRASH), physical aggressiveness (derived AQ); lifestyle	experienced more symptoms of depression and anxiety during the lockdown. They showed more frequently changes of sleep patterns, weight gain, and tobacco consumption than HC. Individuals with depression and/or anxiety were more distressed and concerned about the future, suffered from more sleeping problems, and exercised more than individuals with SZ or BD.	survey, lack of longitudinal follow-up, possible gender bias, questionnaires were only based on validated scales and not these scales themselves were used
Somer *et al*[80]	Mostly in the United States, Italy, Turkey, UK, and Canada, mid-April–mid-May 2020 (during the lockdown)	MDD, anxiety disorder, MD	Cross-sectional online survey of 326 individuals with MD and 546 HC (417 with anxiety disorders, 226 with MDD, and 189 with others in both groups); MDS-16, COVID-19-related variables: Questions about changes in daydreaming and psychosocial functioning	Individuals with depression and anxiety, who were suspected to have MD, were feeling an elevated urge to daydream during the pandemic and had more problems controlling it than individuals with MD and none of these disorders.	No generalizability due to sampling limitations, cross-sectional design does not allow the determination of causality, low effect size, no clinical diagnosis of MD
Van Rheenen *et al*[75]	Australia, April 1-4, 2020 (during the lockdown)	Affective disorders (BD and MDD)	Cross-sectional online survey of 1292 participants with a self-reported affective disorder and 3167 HC; DASS-21, PANAS, COVID-related variables: Questionnaires about primary concerns, changes in personal situation, perceptions, or behaviour	Individuals with affective disorders reported higher psychological distress than HC. Individuals with BD experienced more stress and depressive symptoms compared to individuals with depression; men with BD had more symptoms of distress and depression than women. Both groups did not differ in their mild symptoms of anxiety. Individuals with BD showed more pronounced financial concerns than individuals with depressive disorder and HC.	Self-selection and potentially selection bias, cross-sectional design led to a retrospective self-analysis of changes by the participants with no validation by the authors, self-reported affective disorders, mood disorder group was not balanced regarding gender distribution, no baseline measures of mood and lifestyle
Winkler *et al*[8]	Czech Republic, November 2017 and May 6– 20, 2020 (during and shortly after the lockdown)	Affective disorders (BD and MDD), anxiety disorders, and AUD	Two cross-sectional interviews of 3306 participants in 2017 (10.84% with AUD, 7.79% with anxiety disorders, and 6.57% with affective disorder) and 3,021 in 2020 (18.58% with affective disorder, 12.84% with anxiety disorders, and 9.88% with AUD); MINI, COVID-19-related variables: Lifestyle, worries, seeking of mental professional help, psychiatric symptoms	In 2020, 29.63% of individuals in Czech Republic suffered from mental illness in comparison to 20.02% in 2017. The prevalence of MDD tripled and there was no difference in the prevalence of alcohol use disorder, however, more individuals exhibited binge drinking behavior (4.07% *vs* 6.39%). The suicide risk rose from 3.88% to 11.88% in 2020. Having a mental disorder was associated with more worryies about COVID-19-related impacts on health and economy.	No cohort study and therefore no assessment of the development of mental illness in previously health individuals, lack of face-to-face interviews, relaxation of MINI criterion, data collection after loosening of strictest COVID-19-related measures
Zhu *et al*[51]	China, 28 February-6 March, 2020 (during the lockdown)	SMI	Cross-sectional online survey of 925 inpatients with SMI (657 with SZ and 268 with affective disorder) in economically less developed geographic regions; clinical characteristics, COVID-19-related variables: Self-constructed questions about prevention, knowledge, information sources	The majority of participants (84.4%) had a positive stance regarding measures for preventing COVID-19, which was related to marriage and a higher level of education. The latter was additionally associated with more knowledge about the pandemic. The main sources of information were public media and individuals' attending physicians.	Lack of an outpatient control group, lack of examination of variables associated with attitude and knowledge pertaining COVID-19
Zou *et al*[66]	China, May 22-July 15, 2020 (during and after the lockdown)	SMI, organic mental disorders, and others	Cross-sectional online survey of 1063 older (age ≥ 50 yr) psychiatric patients (485 with MDD, and 578 with BD, SZ, organic mental disorders, and others); Patient Health Questionnaire (PHQ-9), ISI, NPRS, WHOQOL-BREF, self-constructed questionnaires to measure fatigue, COVID-19-related variables: Access to psychiatric services, treatment adherence, concerns	Nearly half of participants were feeling fatigue (47.1%), which was associated with a lower quality of life. A higher level of fatigue was related to more severe symptoms of depression, insomnia, and pain.	Results cannot be generalized, as the patients were of older age, cross-sectional design does not allow the determination of causality, several factors of importance were not researched due to logistical reasons

BD: Bipolar disorder; HC: Healthy controls; MDD: Major depressive disorder; OCD: Obsessive-compulsive disorder; PTSD: Post-traumatic stress disorder; SMI: Serious mental illness; questionnaires: AQ: Aggression Questionnaire; ASRM: Altman Self-Rating Mania Scale; BAI: Beck Anxiety Inventory; BCIS: Believing COVID-19 Information Scale; BDI-II: Beck Depression Inventory II; BDSI: Body Dysmorphic Symptoms Inventory; BRCS: Brief Resilient Coping Scale; BRS: Brief Resilience Scale; CAHSA: Continuum of Auditory Hallucinations-State Assessment; CAPE-42: Community Assessment Psychic Experiences; CES-D: Center for Epidemiologic Studies Depression Scale; CGI: Clinical Global Impression; CPSS: Chinese Perceived Stress Scale; CRASH: Cognitive Reserve Assessment Scale in Health; CSS: COVID Stress Scales; DASS-21: Depression; Anxiety; and Stress Scale-21 Items; DJGLS: De Jong Gierveld Loneliness Scale; EDE-Q: Eating Disorder Examination-Questionnaire – 2nd Ed.; EGS-R: Posttraumatic Stress Disorder Symptom Severity Scale-Revised; FCV-19S: Fear of COVID-19 Scale; FES: Family Environment Scale; GAD-7: Generalized Anxiety Disorder-7; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; IES(-r): Impact of Event Scale(-revised); HRQoL: Health-related quality of life; ISI: Insomnia Severity Index; K10: Kessler 10 Psychological Distress Scale; LS: Loneliness Scale; MADRS: Montgomery-Asberg Depression Rating Scale; MDS-16: Maladaptive Daydreaming Scale; MINI: Mini International Diagnostic Interview; MOS-SS: Medical Outcomes Study Sleep; NEO-FFI: NEO-Five Factor Inventory; NPRS: Numeric Pain Rating Scale; PANSS: Positive and Negative Syndrome Scale; PCIBS: Preventive COVID-19 Infection Behaviours Scale; PCL-C: PTSD Checklist – Civilian Version; PHQ-4/8/9: Patient Health Questionnaire-4/8/9; PMS: Pearlin Mastery Scale; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; PSWQ: Penn State Worry Questionnaire; QIDS: Quick Inventory of Depressive Symptoms; RS-14: Resilience Scale; SCID-5: Structured Clinical Interview for DSM-5; SIAS: Social Interaction Anxiety Scale; SPEQ: Specific Psychotic Experience Questionnaire; SPS: Social participation scale; SPhS: Social Phobia Scale; SRS: Stress-Related Somatic complaints; SSS-S: Self-Stigma Scale-Short; STAY-YA: Spielberger's anxiety questionnaire (French: L'échelle d'anxiété état de Spielberger); SUMD: Scale to Assess Unawareness of Mental Disorder; TEMPS-A: Temperament evaluation of Memphis, Pisa, Paris, and San Diego-autoquestionnaire; UC: Utrechtse Copinglijst; WHOQOL-BREF: World Health Organization Quality of Life-brief version; WI: Whitely Index; Y-BOCS: Yale-Brown Obsessive Compulsive Scale – Symptom Checklist; YMRS: Young Mania Rating Scale.

Individuals with MDD were worried about their health and felt the need for more therapeutic support[58]. Numerous studies found more symptoms of depression[25,42,62,70,71], anxiety[42,62,70,72], PTSD[42,70,72], problems of sleep[70-72], stress[62,72], suicidality, anger, impulsivity[72], worry, loneliness[25], and elevated substance consumption[71] in patients with MDD compared to either HC or measured symptoms before the pandemic. MDD was a predictor of severe distress[73], which was connected to pandemic-related news[74]. Individuals with BD experienced more stress and depressive symptoms than those with MDD, with men having more severe depressive symptoms than women[75].

Individuals with SZ reported to be less stressed during the COVID-19 pandemic than HC[76] and had the least amount of problems with a lack of information about COVID-19 in comparison to other psychiatric disorders[63]. However, they were apparently both more anxious and worried about the current situation and perceived the risk of being infected with COVID-19 as higher than HC[76].

In comparison to individuals with SZ, patients with affective disorders were experiencing more feelings of vulnerability[63]. Furthermore, correlations between high CGI scores and stress-related somatic problems were especially increased in individuals with affective disorders, but could not be found in individuals with SZ[68]. Compared with BD and SZ, individuals with MDD were more worried about contracting the virus[64,77] and had more concerns about service disruption[64]. Furthermore, they were more concerned about the future, suffered from more sleep problems, and exercised more[56].

What are risk and protective factors that influence the severity of psychiatric symptoms and who is particularly vulnerable to these factors?

Regarding SMI in general, it was found that participants experiencing a worsening of psychiatric symptomatology were mainly elderly individuals[78] or had been hospitalized at a more recent date than the individuals who remained stable[36]. Nearly half

of them were experiencing fatigue, which was related to a lower quality of life[66]. However, most of elderly individuals with SMI experienced less psychiatric symptoms [79], approved of the strict governmental measures, and were not afraid of being infected with COVID-19. A higher level of fear was associated with more symptoms of depression, anxiety, stress, and less frequent behavior concerning prevention in older patients with SMI[50]. One study investigating elderly individuals with MDD found a lower quality of life, but not increased symptoms of depression and anxiety[77]. On average, younger patients experienced worse overall health, were feeling more fearful, and had more difficulties adapting than older patients[63]. Additionally, young age was related to increased anxiety and financial concerns in individuals with affective disorders[69].

Stress and distress in individuals with affective disorders were related to a longer duration of psychiatric illness, living alone during the lockdown, the habit of smoking, and frustration, which was associated with unemployment[69]. Especially younger individuals were concerned about pandemic-related consequences regarding their health[8] and socioeconomic status[67,69].

Concerning BD, symptoms of posttraumatic stress were related to anxiety and both work and financial difficulties in the wake of the pandemic. Acute manic symptoms seemed to be protective[42]. Loneliness, not having children, a passive coping style, low mastery, and neuroticism were associated with more psychiatric symptoms[79]. One study found that men had depressive symptoms to a greater extent than women [75]. Individuals with MDD and maladaptive daydreaming were feeling an elevated urge to daydream during the pandemic and had more problems controlling it[80].

Individuals with SZ living in isolation due to a suspected COVID-19 infection were more stressed, anxious, depressed[81], and had a worse quality of sleep than individuals with SZ who were not quarantined[82]. After the quarantine, this symptomatology continued[81]. When living in communal residencies, they were supported by both their cohabitants and mental health professionals, remained adherent to their treatment, and possessed knowledge about the consequences of COVID-19[74].

How does symptomatology and frequency of illness episodes change during the course of the pandemic?

On the one hand, two studies found that psychiatric symptoms remained stable over time in individuals with SMI[57,78], while another one found that the relapse rate did not significantly increase during the pandemic[36]. On the other hand, several studies showed a third of individuals with SMI to exhibit symptoms indicative of a recurrence of their illness or a worsening of symptomatology[52,63].

Pinkham *et al*[57] found that affective symptoms remained stable over time. In contrast, other studies showed that individuals with affective disorders apparently displayed a high likelihood of psychological distress[73,75]. In line with the latter finding, individuals with BD reported to have more psychiatric symptoms compared to the time before the pandemic in one study[75].

The research on MDD was contradictory: On the one hand, few studies showed that individuals with MDD were resilient, mostly socially connected, and did not experience increased symptoms of depression, anxiety, and suicidal ideation[77], with a quarter of them even perceiving an improvement of their mental health during the pandemic in one study[58]. On the other hand, the majority of studies found that individuals with MDD reported both a lower quality of life[70,72,77] and a decrease in mental health compared to the time before the pandemic[58].

Individuals with SZ reported mostly no or only slight changes in their mental health [57,58], and did not find further therapeutic support to be necessary[58].

DISCUSSION

This review is about the impact of COVID-19 on the mental health situation of individuals with BD, MDD, and SZ, gaining data from 19 different countries and areas. In the first months of the crisis, individuals with mental disorders experienced, on average, more pronounced psychiatric symptoms. Nevertheless, some studies showing a reduction of psychiatric symptomatology were found as well. Individuals with affective disorders showed an impairment in mental health, while those with SZ seemed to be mostly unaffected by the pandemic on a mental level. Overall, older patients experienced fewer decline in mental health than younger patients.

First and foremost, contradictory results about the impact of the pandemic on individuals with mental illness in general were found, showing both an increase and a decrease in psychiatric symptoms during the pandemic. The latter was reported more often, showing most commonly symptoms of depression, anxiety[56,59,60], and stress [58-62]. Notwithstanding, these results suggest that individuals with SMI were less affected by the pandemic than HC[25]. This observation was made by numerous authors researching not only individuals with SMI but mental illness in general[27,83] and might be applicable to this specific subgroup as well. The reason for this might be that individuals with mental disorders may be more used to periods of physical distancing and emotional upheaval due to disorder episodes, as Pan *et al*[25] similarly described. For HC, the pandemic has been a more drastic experience, severely influencing their daily lives and therefore leading to more pronounced symptoms of mental illness and a "normal"[25] reaction to this crisis. However, these results only feature the beginning of the COVID-19 pandemic, and the long-term effects on both HC and individuals with mental disorders require continued research.

While individuals with MDD were generally more worried about the pandemic and practiced more preventive behavior[62,77], those with BD seemed to suffer from more depressive symptoms without being as proactive about changing their situation[75]. Factors associated with higher levels of distress were largely connected to lifestyle[73] and socioeconomic environment[69], emphasizing the influence of these factors as well as the importance of outside help and a stable social network[35]. Unemployment was a particularly important factor, as it was related to frustration, anxiety, and bad mood [69], possibly leading to heightened fear about socioeconomic consequences[67]. Individuals with affective disorders are known to have a lower socioeconomic status and higher rates of unemployment than HC[84], making them more vulnerable for mental health degeneration in times of financial instability. In this context, the concept of resilience and strengthening it in individuals with psychiatric disorders, especially in individuals with BD, should be kept in mind for future interventions[85].

Although those diagnosed with SZ were more worried and anxious than HC[76], they seemed to be least affected by the crisis on a mental level among individuals with SMI, as the majority of SZ patients reported only little or no changes in their mental health[57,58,68]. This was explained by both a small sample size[58] and a disregard for "mundane worldly business"[68]. Possibly, they were indeed more preoccupied with their inner world, not focusing particularly on what happened during the pandemic. This coincides with the results about their apparent acceptance of a lack of information about COVID-19[63]. In addition, individuals with SZ reported support from their social network[76], helping them to lessen the mental burden in the wake of the pandemic.

Interestingly, more case reports were found about the exacerbation of SZ than of affective disorders, but these were not included in this review. This could be indicative either of a particular interest in such cases or an increased frequency of them. The latter may be explained by the diathesis-stress model[86], according to which environmental triggers can influence psychiatric symptoms of SZ. Amongst other factors, stress and the subsequent increase in cortisol levels lead to an increased release of dopamine[86,87]. Moreover, exacerbation might be associated with COVID-19 infection. Some patients who were infected were taking clozapine[87-89], which supports the hypothesis of this widely used drug increasing the risk for infection with COVID-19[90,91]. Likewise, stress, depression, and anxiety occurring in SZ patients with COVID-19 might advance an exacerbation[81,82]. COVID-19 itself might cause delirium as well[92]. In conclusion, individuals with SZ may not have been profoundly affected, however, they are vulnerable, especially in case of an infection, which could lead to an exacerbation.

Young age seems to be a risk factor for developing more severe psychiatric symptoms during the pandemic. Younger individuals with SMI had worse mental health and more feelings of fear[63] and anxiety[69] than older individuals, who were mostly reported to remain stable[77,79]. A connection of young age to financial concerns could be found[69], which might be related to unemployment, an important factor for the development of mental health problems during the pandemic. Moreover, social relations played an important part in maintaining the mental health of older adults (age > 60 years)[77]. Many of them were perhaps retired, making the measures of physical distancing a less severe change to their lives. After all, unlike younger adults, they did not have to adjust to the abrupt change of working from home instead of daily meeting their co-workers and thereby connecting socially. Additionally, they did not have the burden of caring for their children staying at home as well. Furthermore, resilience, a protective factor, was found to be high in older adults with SMI[77,79]. Resilience is known to rise with age[93], making it a possible reason for the

better coping ability of older individuals with SMI, which indicates the need for increased resilience once again, especially in younger individuals with SMI.

An increased belief in pandemic-related news was found to be associated with both increased[55] and decreased[50] fear in individuals with SMI, which may be related to the nature of information. Regardless of whether these individuals were more or less [53] informed about COVID-19 and its prevention than HC, they were generally more fearful and worried about the pandemic[58,76,77]. This is concerning if it is related to less prevention behavior[50], because individuals with SMI show more vulnerability to infection with COVID-19 than HC[94,95] and should therefore practice strict measures of prevention. Notably, COVID-19 patients with SZ featured a higher in-hospital mortality rate than HC[96,97]. Consequently, it is important for individuals with SMI to be supplied with information about the pandemic of adequate quality, which would lead to decreased fear and encourage them to protect both themselves and others.

Regarding the situation, increased treatment options for individuals with SMI are integral: Recommendations to use telepsychiatry have been made[98-100] and reports about its effectiveness have been given by several authors[101]. This kind of therapy seems to be well suited to face the situation of physical distancing, at least when it comes to patients without acute exacerbation of their condition requiring immediate medical intervention. In the light of elevated concerns about COVID-19-related healthcare shortages in individuals with mental illness[60,64], telepsychiatry gains in significance for easing the worries of these patients and helping them from afar.

Inconsistent results were found across different studies researching whether the mental health situation of individuals with SMI increased or decreased, although the latter was reported more often. These conflicting outcomes could be explained by cultural, social, and economic background, the pandemic-related situation of different countries, as well as factors pertaining to the implementation of the studies, such as the use of non-standardized questionnaires. Nevertheless, this shows that generalizing the results might not be possible in some cases and should be taken into consideration, as many authors mentioned in their studies. Additionally, these discrepancies highlight the need for measuring individuals' socioeconomic situation and other variables influencing their mental health situation. This was done by several authors; however, it would be important to not only report these results, but also use the aforementioned variables as covariates to facilitate international comparison. Further limitations implicate more aspects to be taken into account for future research: The sample should be of adequate size, follow-up studies are needed to research causality and observe long-term effects, and standardized questionnaires about COVID-19-related variables, such as those proposed by Chang *et al*[54], should be used to enable better comparability. Additionally, the conduction of a meta-analysis would be ideal to better evaluate the impact of the pandemic on individuals with SMI.

CONCLUSION

The pandemic and its consequences have been leading to a decrease in the mental health situation of individuals with SMI across the world, especially those with affective disorders. Increasing symptoms of anxiety, depression, and stress were most frequent and higher in comparison to HC. Along with age and resilience, the main contributing factors seem to be of socioeconomic nature, with the shortage of treatment options, fear, adequate information, and social support being particularly important. This precarious situation necessitates a reinforcement of mental health services, first and foremost the usage of telepsychiatry. Moreover, it is paramount to supply patients with adequate information about COVID-19 and its prevention and to increase their resilience. Respecting scientific research about psychiatric disorders, both standardizations to enable generalization of results and the conduction of long-term follow-up studies are integral to further investigate SMI.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) is greatly influencing the mental state of individuals from all walks of life. Individuals with serious mental illness (SMI: bipolar disorder, major depressive disorder, and schizophrenia) are especially vulnerable to the reverberations of such a crisis, leading among other symptoms to an increase of

depression and anxiety. The pandemic is an excellent opportunity to broaden the understanding of these disorders and improve methods of treatment.

Research motivation

Individuals with SMI having been researched in the course of several studies calls for a coherent analysis of all findings to gain an insight in the mind of these individuals, making their support more efficient. At the time of the search, no other review focusing on solely the clinical characteristics of individuals with SMI had been published in the searched databases.

Research objectives

This review aimed to assess the situation of individuals with SMI and their mental state during the COVID-19 crisis. The following questions were answered: (1) How are individuals with SMI affected by the pandemic in comparison to healthy controls (HC) and what are the main psychiatric symptoms they are displaying? (2) What are risk and protective factors that influence the severity of psychiatric symptoms and who is particularly vulnerable to these factors? And (3) How does symptomatology and frequency of illness episodes change during the course of the pandemic?

Research methods

We systematically searched MEDLINE and PubMed (day of the final search: January 9, 2021), including terms related to the impact of the COVID-19 pandemic on the mental health of individuals with bipolar disorder, major depressive disorder, and schizophrenia. Only studies providing original data were included.

Research results

The search yielded 36 studies. The impact of the COVID-19 pandemic generally affected the mental health of individuals with SMI in a negative way, with individuals with affective disorders being more impacted than those with schizophrenia. The most common symptoms were those of depression, anxiety, and stress. Mental health was mainly influenced by age, resilience, and socioeconomic circumstances, particularly the shortage of mental health services, lack of social support, and inadequate information about COVID-19.

Research conclusions

Mental health services, particularly telemental health services, should be reinforced to better support individuals with SMI and strengthen their resilience. Moreover, individuals with SMI should be supplied with information about the pandemic and the employment of protection measures.

Research perspectives

Future research requires follow-up studies to determine causality and long-term effects, greater sample sizes, and standardization.

ACKNOWLEDGEMENTS

A sincere thank you to Ms. Nina Bonkat for her diligent proofreading of this paper.

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatr 2021 December 19; 11(12): 1407-1424

DOI: 10.5498/wjp.v11.i12.1407

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Psychoeducation in bipolar disorder: A systematic review

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Author contributions: Barbosa IG designed the research study; Rabelo JL and Barbosa IG performed the research, analyzed the data and wrote the manuscript; Cruz BF and Viana BM revised the analysis and wrote the manuscript; Ferreira JDR contributed to the discussion.

Conflict-of-interest statement: There is no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Brazil

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

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Abstract

BACKGROUND

Bipolar disorder (BD) is a severe psychiatric disorder characterized by mood swings. Psychosocial interventions, such as psychoeducation, play an essential role in promoting social rehabilitation and improving pharmacological treatment.

AIM

To investigate the role of psychoeducation in BD.

METHODS

A systematic review of original studies regarding psychoeducation interventions in patients with BD and their relatives was developed. A systematic literature search was performed using the Medline, Scopus, and Lilacs databases. No review articles or qualitative studies were included in the analysis. There were no date restriction criteria, and studies published up to April 2021 were included.

RESULTS

A total of forty-seven studies were selected for this review. Thirty-eight studies included patients, and nine included family members. Psychoeducation of patients and family members was associated with a lower number of new mood episodes and a reduction in number and length of stay of hospitalizations. Psychoeducational interventions with patients are associated with improved adherence to drug treatment. The strategies studied in patients and family members do not interfere with the severity of symptoms of mania or depression or with the patient's quality of life or functionality. Psychoeducational interven-

Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

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Received: March 3, 2021
Peer-review started: March 3, 2021
First decision: June 5, 2021
Revised: June 11, 2021
Accepted: November 13, 2021
Article in press: November 13, 2021
Published online: December 19, 2021

P-Reviewer: Gazdag G, Li XM
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

tions with family members do not alter patients' adherence to pharmacotherapy.

CONCLUSION
Psychoeducation as an adjunct strategy to pharmacotherapy in the treatment of BD leads to a reduction in the frequency of new mood episodes, length of hospital stay and adherence to drug therapy.

Key Words: Bipolar disorder; Mood disorders; Psychoeducation; Adherence; Mania; Depression

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Core Tip: Bipolar disorder (BD) is a severe and chronic psychiatric disorder that requires intense treatment usually based on pharmacotherapy. Treatment applying psychotherapy adjunctive treatment is usually prescribed, although with inconsistent data. We aimed to perform a systematic review evaluating the evidence of psychoeducation in BD patients and their family members. Evidence suggests that psychoeducation of patients and family members is associated with a lower number of new mood episodes and a reduction in number and length of stay of hospitalizations. Psychoeducational interventions with patients are associated with improved adherence to drug treatment. Psychoeducation is a good interventional strategy for BD treatment.

Citation: Rabelo JL, Cruz BF, Ferreira JDR, Viana BM, Barbosa IG. Psychoeducation in bipolar disorder: A systematic review. *World J Psychiatr* 2021; 11(12): 1407-1424
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1407.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1407

INTRODUCTION

Bipolar disorder (BD) is a chronic mental health illness characterized by mood swings [1]. It is estimated that more than 1% of the world population is affected by BD[2,3]. The prevalence rates for each BD subtype, I and II, in community-based samples are 0.6% and 1.4%, respectively, and the mean age of onset of the disease is approximately 20 years[2,3]. Poor treatment adherence is associated with mood swings, social stigmatization, and lower social support in BD[4]. Psychosocial interventions might play an essential role in promoting social rehabilitation and improving pharmacotherapy adherence. Studies have demonstrated that non-pharmacological interventions, such as psychoeducation and cognitive-behavioral and interpersonal therapy, promote effects in the treatment of acute mood episodes and maintenance treatment in BD[5]. These actions favors the early recognition of warning signs of mood instability and promote the development of healthier lifestyles[4].

Psychoeducation is an intervention strategy based on providing patients and/or relatives with information about the disorder to enhance their understanding and enable early identification of warning signs and mood changes, improving treatment adherence[5-7]. Psychoeducational strategies in BD might promote the frequency of new mood episodes and medication adherence[8]. The Barcelona Psychoeducation Program was associated with an almost ninefold decrease ratios regarding new mood episodes and reduced the number of symptomatic days, as well as the hospitalization's length of stay (LOS)[9]. Family psychoeducation intervention has been correlated with mood episode reduction in patients with BD[7]. When family members acquire better knowledge about the disorder, they contribute to the early detection of the first symptoms of changes in mood[10,11].

This systematic review aims to investigate the role of psychoeducation in BD in patients and in their family members.

MATERIALS AND METHODS

Search strategies and selection criteria

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist. A systematic literature search was performed through the Medline (Medical Literature Analysis and Retrieval System Online/PubMed), Scopus and Lilacs databases. Studies published up to April 2021 were included. The key terms used were "bipolar disorder" and "psychoeducation". Studies in Portuguese and English were selected. Two independent reviewers (J.L.R. and I.G.B) analyzed the titles and abstracts; afterward, texts that fulfilled the requirements were included. The inclusion criteria were as follows: (1) Original psychoeducation intervention studies; (2) Placebo-controlled studies; and (3) Interventions aimed at adult patients with BD. The exclusion criteria were as follows: (1) Review, case series, and case report; (2) Interventions aimed at groups of patients with other mental or behavioral disorders; (3) Book chapters or reviews, systematic reviews or meta-analyses; (4) Studies written in languages other than English or Portuguese; (5) Low-quality studies according to the Newcastle–Ottawa scale (NOS) scale; and (6) Interventions aimed at children or adolescent patients with BD. Only original studies with a control group or baseline data for psychoeducation interventions in patients with BD and their relatives were included.

Data extraction and quality assessment

The systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42020168910.

We developed a data extraction table based on a Cochrane model[12]. One of the revisors (J.L.R.) extracted data and another (I.G.B) verified them. To reduce selection bias, two revisors (J.L.R. and I.G.B.) assessed the methodological quality of all the studies according to the NOS criteria[13]. The NOS is a "star system"-based scale, which scores a maximum of 4 stars corresponding to selecting studying groups, 3 stars for the ascertainment of either the exposure or outcome of interest, and 2 for the comparability of the groups; thus, the total NOS maximum score is 9. In the present study, we considered a minimum score of 5 on the NOS scale sufficient to be included [13]. In the circumstances of any disagreement between those 2 revisors, a third revisor was consulted (B.F.C) for consensus.

All extracted data included information about publication (including author name and year of publication), some group characteristics (sample size, gender, mean age, mood state and subtype of BD), methods (psychoeducation protocols; number of sessions; instruments that were applied, and who had performed them; kind of study, either a blinded or a randomized one) and their main outcomes.

RESULTS

Description of studies

Six hundred sixty-seven publications were identified from the literature search (PubMed: Five hundred and eighty-four; Scopus: Sixty-one and Lilacs: Twenty-four). Duplicated studies were excluded (n = 34). Five hundred thirty-nine were excluded after title and abstract screening. Twenty studies were included from manual extraction. Seventy-two studies were excluded: Four of these were article reviews; thirty-seven did not include psychoeducation treatment; four were about intervention strategies in patients under 18 years of age; five studies were qualitative studies; one study was about a protocol; and thirteen studies were duplicated. Eight studies were classified as low quality according to the NOS scale (*i.e.*, scored less than or equal to five stars) and were excluded from the present manuscript. A total of forty-seven publications were selected for this review, of which thirty-eight studies included patients with BD and nine studies included relatives of patients with BD (Figure 1).

Characterization of included studies

Studies in patients with BD: Thirty-eight clinical studies were included. Thirty-eight studies[6,8,11-46] scored five or more stars according to the NOS scale[12] (Table 1). There were thirty-three randomized studies[6,8,11-18,20-26,28-32,34-36,39-47] and five nonrandomized studies[19,27,33,37,38]. Eighteen studies included euthymic or remitted patients[6,8,11,16-21,25,26,28,33,35,37,41-43]. Two studies included patients with depressed mood[31,32]. Sixteen publications did not evaluate the mood episodes

Table 1 Newcastle–Ottawa scale evaluation for studies that assessed psychoeducation in bipolar disorder patients

Ref.	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total
Zhang *et al*[14], 2019	1	1	1	1	2	1	1	1	9
Wiener *et al*[15], 2017	1	1	1	1	1	1	1	1	8
Cardoso *et al*[16], 2015	1	1	1	1	1	1	1	1	8
Cardoso *et al*[17], 2014	1	1	1	1	1	1	1	1	8
Faria *et al*[18], 2014	1	1	1	1	2	1	1	1	9
Kurdal *et al*[19], 2014	1	1	1	1	1	1	1	1	8
Javadpour *et al* [20], 2013	1	1	1	1	2	1	1	1	9
de Barros Pellegrinelli *et al* [21], 2013	1	1	1	1	2	1	1	1	9
Candini *et al*[22], 2013	1	1	1	1	1	1	1	1	8
Colom *et al*[11], 2009	1	1	1	1	2	0	1	1	8
Colom *et al*[23], 2003	1	1	1	1	2	1	1	2	10
Colom *et al*[24], 2003	1	1	1	1	2	1	1	1	9
Dalum *et al*[25], 2018	1	1	1	0	1	0	1	1	6
Depp *et al*[26], 2015	1	1	1	1	1	1	1	1	8
Lauder *et al*[27], 2015	1	1	1	1	1	1	1	1	8
Torrent *et al*[28],	1	1	1	1	2	1	1	1	9

2013									
Smith *et al*[29], 2011	1	1	1	1	2	1	1	1	9
Sylvia *et al*[30], 2011	0	1	1	1	2	1	1	0	6
D'Souza *et al*[31], 2010	1	1	1	1	2	1	1	1	9
Castle *et al*[32], 2010	1	1	1	1	2	0	1	1	8
So *et al*[46], 2021	1	1	1	1	1	0	1	1	7
Sajatovic *et al*[33], 2009	1	1	1	1	2	1	1	1	9
Miklowitz *et al* [34], 2007	1	1	1	1	2	0	1	0	7
Miklowitz *et al* [35], 2007	1	1	1	1	2	1	1	1	9
González Isasi *et al* [36], 2014	1	1	1	1	1	1	1	1	8
Parikh *et al*[37], 2012	1	1	1	1	2	1	1	1	9
Zaretsky *et al*[38], 2008	1	1	1	1	1	1	1	1	8
Proudfoot *et al* [39], 2012	1	1	1	1	1	1	1	1	8
Aubry *et al*[40], 2012	1	1	1	1	1	0	1	0	6
Gonzalez *et al*[41], 2007	0	1	1	1	2	1	1	1	8
Miklowitz *et al* [42], 2003	1	1	1	1	1	1	1	1	8
Petzold *et al*[45], 2019	1	1	1	1	1	1	1	1	8
Pakpour *et al*[43], 2017	1	1	1	1	1	1	1	1	8
Morris *et al*[7], 2016	1	1	1	1	1	1	1	1	8

Kessing *et al*[44], 2014	1	1	1	1	1	1	1	1	8
Gumus *et al*[47], 2015	1	1	1	1	1	1	1	1	8
Eker *et al*[48], 2012	1	1	1	0	1	0	1	1	6
Perry *et al*[49], 1999	1	1	1	1	2	1	1	1	9

of the patients[12-15,22-24,27,29,30,34,36,38-40,44].

The DSM-IV diagnostic criteria for BD were applied in twenty-nine studies[6,8,11,12,15,16,18-21,23-26,29-35,37,40,42,43,46,47]. The DSM-III was applied in four studies [13,27,39,44], and the ICD-10 criteria were applied in two studies[22,41]. One study did not state its diagnostic criteria for BD diagnosis[17].

A total of 2721 patients with BD and 1107 controls were included. Patients were classified as having type I or II BD in twenty-four studies[6,8,11,17-20,23-27,29-32,34,35,37,38,40,42,46,47]. Six studies evaluated BD type I patients[21,28,33,39,41,45], and only one study assessed BD type II patients[15].

Psychoeducation programs in patients with BD: Psychoeducation interventions and outcomes are summarized in Table 2. Eleven studies[11,15-24] assessed the psychoeducation manual for BD (PMBD)[6]. Patients in the PMBP group presented a lower incidence of new mood episodes, fewer hospitalizations[11,23,24], and reduced LOS[11,21,24]. Patients in the PMBD group had a reduction in the number of depressive episodes[17,18,23]. No difference was observed in the number of mood episodes in four studies[15,16,18,21]. PMBD was associated with a higher adherence to pharmacological treatment and a higher quality of life in one study[20]. PMDB did not result in better functional parameters[19,21].

Eight studies evaluated Group psychoeducation (GP)[45-51]. BD included in the GP compared to controls exhibited a longer interval between mood episodes[44], higher adherence to pharmacological treatment[45,46], and lower rates of hospital admissions [44]. GP interventions were not associated with functional, social or family improvements[46].

Intensive psychosocial intervention was not associated with functional state improvement[35], mood episode frequency[33], or new mood episodes (Hamilton depression rating scale). One study showed a reduction in the number of hospitalizations and mean hospitalization time[37].

Other psychoeducational techniques were applied in eleven studies[11,22-24,26-29,36,38,39]. Illness Management and Recovery program (IMR)[22]; Family-focused treatment (FFT)[42]; Systematic Illness Management Skills Enhancement Programme BD (SIMSEP-BD)[31] and MoodSwings-Plus (MS-PLUS)[27] were associated with increased adherence to pharmacological treatment. Nutrition/weight loss, exercise, and wellness treatment (NEW Tx)[30] and Personalized Real-Time Intervention for

Table 2 Extracted data from studies that evaluated psychoeducation in patients with bipolar disorder

Ref.	BD	Sample size, N (P × C)	Age in years (P × C)	Female frequency (%) (P × C)	Intervention	Applied scales/parameters	Results
Zhang *et al*[14], 2019	I e II	35 × 39	34.2 × 34.6	57.1 × 46.2	SCIT	YMRS	$P = 0.21$
						HDRS	$P = 0.11$
						FAST	$P < 0.001$
						TMTA	$P = 0.77$
						SDMT	$P = 0.09$
						HVLT-R	$P = 0.09$
						SCWT	$P = 0.054$
Wiener *et al*[15], 2017	ND	32 × 29	24 × 23.81	83.3 × 76.2	PMBD	HDRS	$P = 0.028$
						YMRS	$P = 0.879$
Cardoso *et al*[16], 2015	ND	32 × 29	24.09 × 24.03	65.6 × 72.4	PMBD	BRIAN	$P = 0.88$
						HARS	$P = 0.175$
						YMRS	$P = 0.576$
						HDRS	$P = 0.074$
Cardodo *et al*[17], 2014	ND	32 × 29	24.09 × 24.03	65.6 × 72.4	PMBD	HDRS	$P = 0.001$
						YMRS	$P = 0.102$
Faria *et al*[18], 2014	II	32 × 29	24.09 × 24.03	72.4 × 65.6	PMBD	BRIAN	$P = 0.01$
						Depressive symptoms	$P = 0.001$
Kurdal *et al*[19], 2014	ND	40 × 40	37.17 × 33.9	35 × 40	PMBD	BDFQ	$P > 0.005$
Javadpour *et al*[20], 2013	I e II	45 × 41	24.4/23.2	23 × 21	PMBD	WHOQOL-BREF	$P < 0.001$
						MARS	$P = 0.008$
						Hospitalizations	$P < 0.001$
de Barros Pellegrinelli *et al*[21], 2013	I e II	32 × 23	43.43 × 43.74	23 × 15	PMBD	HDRS	$P = 0.820$
						YMRS	$P = 0.716$
						SAS	$P = 0.114$
						GAF	$P = 0.586$
						CGI	$P = 0.026$
Candini *et al*[22], 2013	I e II	57 × 45	41.5 × 44.8	52.6 × 48.9	PMBD	Hospitalizations	$P = 0.001$
						Number of days of hospitalization	$P = 0.001$
Colom *et al*[11], 2009	I e II	60 × 60	34.03 × 34.26	63.3 × 63.3	PMBD	New mood episode	$P = 0.002$
						Hospitalizations	$P = 0.023$
						Number of days of hospitalization	$P = 0.047$
Colom *et al*[23], 2003	I	25 × 25	35.36 × 34.48	64 × 60	PMBD	Mood episodes in the treatment phase	$P = 0.003$
						Mood episodes after 2 yr	$P = 0.008$
						Depressive episodes	$P = 0.004$
						Hospitalizations	$P = 0.001$
Colom *et al*[24], 2003	I e II	60 × 60	23.25 × 22.26	63.3 × 63.3	PMBD	New mood episode	$P = 0.001$
						Hospitalizations	$P = 0.05$

						Number of days of hospitalization	$P = 0.05$
Dalum *et al*[25], 2018	ND	23 × 24	41 × 45	46 × 44	IMR	IMRS-P	$P = 0.14$
						IMRS-S	$P = 0.76$
Depp *et al*[26], 2015	I e II	51 × 63	46.9 × 48.1	53.7 × 63.4	PRISM	YMRS	$P = 0.004$
						MADRS	$P = 0.036$
						IIS	$P = 0.636$
Lauder *et al*[27], 2015	I e II	71 × 59	39.87 × 41.35	73 × 76	MS–PLUS	ASRMS	$P = 0.02$
						MADRS	$P = 0.003$
						MOS-SSS	$P = 0.003$
						MARS	$P = 0.001$
						GPF	$P = 0.003$
Torrent *et al*[28], 2013	I e II	159 × 80	40.59 × 40.47	57.1 × 57.5	FR	FAST	$P = 0.002$
						HDRS	$P > 0.05$
						YMRS	$P > 0.05$
						Hospitalizations	$P > 0.05$
Smith *et al*[29], 2011	I e II	24 × 26	42.7 × 44.7	54.2 × 69.2	BBO	FAST	$P = 0.15$
						GAF	$P = 0.21$
						SAI	$P = 0.44$
						WHOQOL-BREF	$P = 0.25$
Sylvia *et al*[30], 2011	I e II	4 × 6	60 × 50.2	75 × 33	NEW TX	MADRS	$P = 0.10$
						LIFE-RIFT	$P = 0.014$
D'Souza *et al*[31], 2010	I	27 × 31	40.7 × 39.5	51.85 × 51.61	SIMSEP-BD	ARS	$P = 0.001$
						New mood episode	$P = 0.015$
						Time between mood episodes	$P = 0.001$
Castle *et al*[32], 2010	I e II	42 × 42	41.6 × 42.6	79 × 26	MAPS	Mood episode	$P = 0.003$
						Depressive symptoms	$P = 0.003$
						Knowledge about illness	$P > 0.05$
						ESM-PA	$P = 0.024$
						ESM-NA	$P = 0.001$
So et *et al*[46], 2021	I e II	38 × 26	35.8 × 43.1	78.9 × 73.1	LGP	Medication adherence	$P > 0.05$
Sajatovic *et al*[33], 2009	I e II	80 × 80	41.13 × 40	73.75 × 87.5	LGP	DAI	$P = 0.366$
						SRTAB	$P = 0.577$
						GAS	$P = 0.382$
Miklowitz *et al* [34], 2007	I e II	163 × 130	40.1 × 40	ND	IPI	Remission of symptoms 1 yr	$P = 0.001$
Miklowitz *et al* [35], 2007	I e II	84 × 68	ND	59 × 59	IPI	LIFE-RIFT	$P = 0.006$
González Isasi *et al* [36], 2014	I	20 × 20	43.35 × 39.25	45 × 50	CBT	STAI-S	$P = 0.062$
						YMRS	$P = 0.009$
						BDI	$P = 0.131$
						IS	$P = 0.001$
Parikh *et al*[37], 2012	I e II	109 × 95	40.9 × 40.9	53.2 × 63.2	CBT	LIFE	$P > 0.05$
						CARS-M	$P = 0.089$

						HDRS	$P = 0.089$
Zaretsky *et al*[38], 2008	I e II	40 × 39	ND	ND	CBT	CARS-M	$P = 0.001$
						HDRS	$P = 0.001$
Proudfoot *et al* [39], 2012	ND	139 × 134	35.3 × 40.9	66.9 × 69.4	BEP	GADS	$P > 0.05$
						WSAS	$P > 0.05$
						SWLS	$P > 0.05$
						BRIEF IPQ	$P = 0.001$
Aubry *et al*[40], 2012	I e II	50 × 35	46 × 52	66 × 62.9	LGP	Hospitalizations	$P = 0.001$
						Number of hospitalizations	$P = 0.009$
Gonzalez *et al*[41], 2007	I e II	11 × 11	40.5 × 41.0	45.45 × 45.45	IOM	GAF	$P = 0.65$
						CGI-BD	$P = 0.06$
						Depressive symptoms	$P = 0.005$
Miklowitz *et al* [42], 2003	I	31 × 70	35.6 × 36.6	58 × 66	FFT	SADS-C	$P = 0.001$
						New mood episode	$P = 0.001$
						MTS	$P = 0.001$
Pakpour *et al*[43], 2017	I e II	134 × 136	41.8 × 41.2	55.2 × 50.7	GP	MARS	$P = 0.001$
						YMRS	$P = 0.001$
						CGI	$P = 0.001$
						QoL.BD	$P = 0.001$
Petzold *et al*[45], 2019	I e II	39 × 34	44.32 × 42.69	43.6 × 47.1	GP	New mood episode	$P = 0.175$
						YMRS	$P = 0.241$
						HDRS	$P = 0.58$
						SF-36	$P = 0.359$
Morriss *et al*[7], 2016	I e II	153 × 151	44.2 × 46 ·5	60 × 56	GP	Time between mood episodes	$P = 0.012$
						SOFAS	$P > 0.05$
						SAS	$P > 0.05$
Kessing *et al*[44], 2014	I	72 × 86	64.1 × 63	61.1 × 48.8	GP	Time between mood episodes	$P = 0.014$
						Hospitalizations	$P = 0.064$
Gumus *et al*[47], 2015	I e II	41 × 41	38.7 × 40.05	40.5 × 56.1	GP	Number of mood episodes	$P = 0.208$
Eker *et al*[48], 2012	ND	35 × 36	34.57 × 36.54	54.3 × 52.8	GP	ANT	$P < 0.005$
						MARS	$P < 0.005$
Perry *et al*[49], 1999	I	34 × 35	44.1 × 45	68 × 69	GP	Time between manic episodes	$P = 0.008$
						Time between depressive episodes	$P = 0.19$

ANT: Attitudes towards neuroleptic treatment; ASRMS: Altman self-rating mania scale; ARS: Medication adherence scale; B: Baseline; BBO: Beating bipolar online; BD: Bipolar disorder; BDG: Bipolar disorder group; BDI: Beck depression inventory; BDFQ: Bipolar Disorder Functioning Questionnaire; BEP: Bipolar Education Program; BDNF: Brain-Derived Neurotrophic Factor; BRIAN: Biological Rhythm Interview of Assessment in Neuropsychiatry; BRIEF IPQ: The Brief Illness Perception Questionnaire; C: Controls; CARS-M: Clinician-Administered Rating Scale for Mania; CBT: Cognitive-behavioral therapy; CC: Collaborative care; CGI-BD: Clinical Global Impression Scale for Bipolar Disorder; DAI: Drug Attitude Inventory; EDM: Education about Disorders and Medications; ESM-PA: With in person positive affect as measured by using Experience Sampling Method; ESM-NA: Within-person negative affect as measured by using Experience Sampling Method; FAST: Functional Assessment Test; FFT: Family-focused treatment; FR: Functional remediation; GADS: The Goldberg Anxiety and Depression Scale; GAF: Global Assessment of Functioning; GAS: Global Assessment Scale; HVLT-R: Hopkins Verbal Learning Tests-Revised; GDNF: Glial cell line-derived neurotrophic factor; GPF: Global Measure of Psychosocial Functioning; GP: Group Psychoeducation; HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; IOM: Integrative Outpatient Model; IMR: Illness Management and

Recovery program; IMRS–P: Illness Management and Recovery Scale–participants' version; IMRS–S: Illness Management and Recovery Scale–staffs; IPI: Intensive Psychosocial Intervention; IS: Maladjustment scale; IRSRT: Interpersonal and social rhythm therapy; LGP: Life Goals Program; LIFE: Longitudinal Interval Follow-up Evaluation; LIFE-RIFT: The Range of Impaired Functioning Tool; MADRS: Montgomery–Asberg Depression Rating Scale; MOSSF-36: Medical Outcomes Survey Short-form General Health Survey; MTS: Maintenance Treatment Scale; MARS: Medication Adherence Rating Scale; MAPS: Monitoring mood and activities (M), assessing prodromes (A), preventing relapse (P) and setting Specific, Measurable, Achievable, Realistic, Time-framed (SMART) goals (S); MARS: Medication adherence rating scale; MS-PLUS: MoodSwings-Plus; MOS-SSS: Medical Outcomes Study Social Support Survey; ND: Not described; NEW TX-Program: Nutrition/weight loss, Exercise, and Wellness Treatment; NGF: Nerve growth factor; P: Patients; PMBD: Psychoeducation Manual For Bipolar Disorder; PRISM: Personalized Real-Time Intervention for Stabilizing Mood , QoL.BD: Quality of Life in Bipolar Disorder scale; SAI: Schedule for Assessment of Insight; SADS-C: Schedule for Affective Disorders and Schizophrenia, Change Version; SAS: Social Adjustment Scale; SCIT: Social cognition and Interaction Training; SCWT: Stroop Color-Word Test; SDMT: Symbol Digit Modalities Test; SIMSEP-BD: Systematic Illness Management Skills Enhancement Program Bipolar Disorder; SF-36: 36-Item Short Form Survey; SOFAS: Social and Occupational Functioning Assessment Scale; SRTAB: Self-reported treatment adherence behaviours; STAI-S: State Trait Anxiety Inventory; SWLS: The Satisfaction with Life Scale; TMTA: Trail Making Test-A; WHOQOL–BREF: World Health Organization Quality of Life, Brief version; WSAS: The Work and Social Adjustment Scale; YMRS: Young Mania Rating Scale.

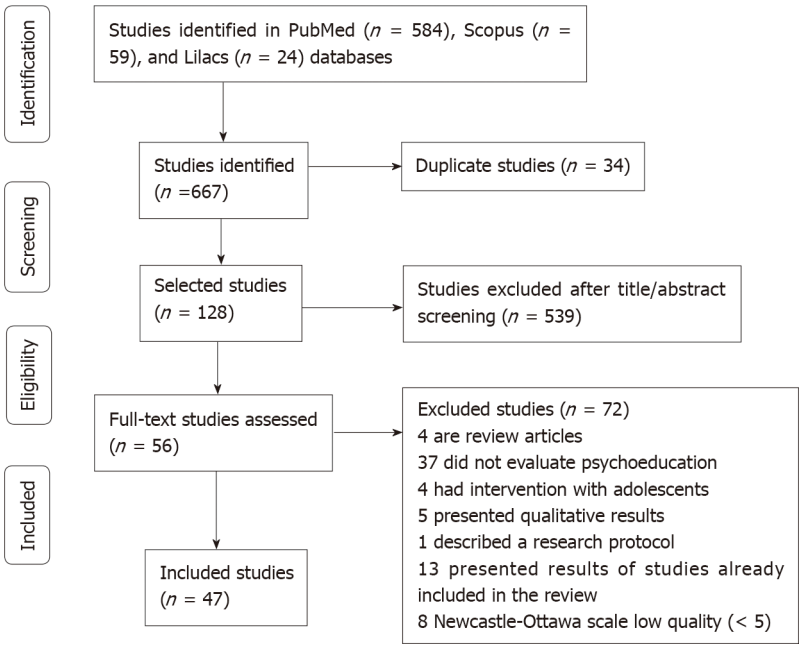


Figure 1 PRISMA flow diagram for studies evaluating psychoeducation in bipolar disorder.

Stabilizing Mood (PRISM)[25] were associated with a reduction in severity of mania symptoms. Depressive symptoms were less severe in patients submitted to MAPS-monitoring mood and activities (M), assessing prodromes (A), preventing relapse (P) and setting Specific, Measurable, Achievable, Realistic, Time-framed (SMART) goals (S)[32], integrative outpatient model (IOM)[38], and PRISM[25] interventions, when compared to control intervention. The online bipolar education program (BEP) was associated with a reduction in anxiety symptoms[39]. There was a reduction in the frequency of mood episodes in patients submitted to IMR[26] and MAPS[33]. Functional remediation (FR) was associated with improvement in functional status [28]. Social cognition and interaction training (SCIT)[14], FR[28], FFT[41], SIMSEP-BD [31], MAPS[32] and MS-PLUS[27] were not associated with changes in the severity of mood symptoms. FR did not influence the number of hospital admissions[28]. BEP [39], Beating bipolar online[29], and IOM[41] did not influence functional status. BEP was not associated with improvement in the quality of life or increased insight[29].

Studies with relatives of patients with BD: Nine clinical studies were included. Nine studies scored five or more stars[50-58] according to the NOS scale[13] (Table 3). There were seven randomized[50-52,54,58] and two nonrandomized studies[53,57]. Two studies evaluated euthymic patients[51,53]. Information regarding mood episodes was not available in seven studies[50-52,55-58].

Four studies diagnosed patients according to the DSM-III criteria[49,51-53], and four studies applied the DSM-IV[46-48,50]. One study did not state the BD diagnostic criteria[50]. Two studies assessed BD type I and BD type II patients[48,50]; three studies included exclusively BD type I patients[46,49,52]. Four studies did not specify

Table 3 Newcastle–Ottawa scale evaluation for studies that evaluated psychoeducation in relatives of patients with bipolar disorder

Ref.	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total
Hubbard *et al* [50], 2016	1	1	1	1	1	1	0	1	7
Fiorillo *et al* [51], 2015	1	1	1	1	1	1	1	0	7
Madigan *et al* [52], 2012	1	1	1	1	1	1	1	1	8
Reinares *et al* [53], 2008	1	1	1	1	1	1	1	1	8
Solomon *et al* [54], 2008	1	1	1	1	1	0	1	0	6
Reinares *et al* [55], 2004	1	1	1	1	1	1	1	0	7
Van Gent *et al* [56], 1991	1	1	1	1	1	0	1	0	6
Miklowitz *et al*[57], 2000	1	1	1	1	1	0	1	1	7
Simoneau *et al* [58], 1999	1	1	1	1	1	0	1	0	6

the BD type[45,47,51,53].

One hundred thirteen relatives were included in psychoeducation programs: one hundred and six were couples; twelve were sons/daughters; and ten were brothers/sisters. Fifty-four parents were included in the control groups, eighty-nine were couples, two were sons/daughters, six were brothers/sisters, and two were friends.

Psychoeducation programs aimed at family members of patients with BD: Psychoeducation interventions and outcomes are summarized in Table 4. Two studies[52,53] compared the program of pharmacotherapy and FFT and Crisis management with naturalistic follow-up (CMNF). There was no difference in the severity of mood symptoms after a one-year follow-up[52]. There was a reduction in the frequency of mood episodes in the FFT compared to the CMNF[52].

Three studies assessed the psychoeducational family intervention (PFI) strategy compared to a nonintervention control group[51,53,54]. There were no improvements in the frequency of mood episodes[50], adherence to treatment[53], or caregiver burden[55]. The group submitted to PFI showed a significant improvement in relation

Table 4 Extracted data from studies that evaluated psychoeducation in relatives of patients with bipolar disorder

Ref.	BD	Psychoeducation group			Group control			Applied scales/parameters	Results
		Psychoeducation strategy	*n* (%)		Intervention strategy	*n* (%)			
Hubbard *et al*[50], 2016	ND	GCPBD	18	8 Partner; 10 Parents	WL	14	3 Partner; 8 Parents; 1 Sibling; 2 Friend	DASS- 21	$P = 0.52$
								BAS	$P = 0.91$
								KBDS	$P > 0.05$
								BDSS	$P > 0.05$
Fiorillo *et al* [51], 2015	BD I	PFI	85	21 Parents; 44 Partner; 10 Son; 9 Sibling; 1 Other	WI	70	23 Parents; 31 Partner; 11 Son; 3 Sibling; 2 Other	Subjective burden	$P = 0.001$
								Professional help	$P = 0.001$
								Help in emergencies	$P = 0.01$
Madigan *et al*[52], 2012	ND	MFGP; SFGP	18; 19	ND	WI	10	ND	Caregiver knowledge	$P = 0.404$
								IEQ	$P = 0.795$
								GHQ12	$P = 0.723$
								WHOQOL Bref	$P = 0.355$
								GAF	$P = 0.617$
Reinares *et al*[53], 2008	BD I e II	PFI	57	35 Parents; 20 Partner; 2 Offspring/siblings	WI	56	27 Parents; 25 Partner; 4 Offspring/siblings	Amount of daily contact between the patient and the caregiver	$P = 0.757$
								Manic/hypomanic recurrence time	$P = 0.015$
								Medication adherence	$P = 0.611$
Solomon *et al*[54], 2008	BD I	MFGP; IFT	21; 16	ND	WI	16	ND	New mood episode	$P = 0.47$
								Hospitalization frequency	$P = 0.04$
								BRMS	$P = 0.44$
								HAM-D	$P = 0.12$
Reinares *et al*[55], 2004	BD I e II	PFI	30	17 Parents; 12 Partner; 1 Sibiling	WI	15	6 Parents; 6 Partner; 2 Son; 1 Sibiling	HAM–D	$P > 0.05$
								YMRS	$P > 0.05$
								Subjective burden of the caregiver	$P = 0.48$
								FES	$P = 0.22$
								Knowledge about the disorder	$P = 0.001$
Van Gent *et al*[56], 1991	ND	GT	14	14 Partner	WI	12	12 Partner	IPSQ	$P > 0.05$
								IPP	$P > 0.05$
								SCL-90	$P > 0.05$
Miklowitz *et al*[57], 2000	BD I	FFT	31	ND	CMNF	70	ND	New mood episode	$P = 0.042$
								Depressive symptoms	$P = 0.06$
								Manic symptoms	$P = 0.59$
Simoneau *et al*[58], 1999	ND	FFT	22	ND	CMNF	22	ND	KPI	$P > 0.05$

BAS: Burden assessment scale; BD: Bipolar disorder; BDSS: Bipolar disorder self-efficacy scale; BPRS: Brief psychiatric rating scale; BRMS: Bech-Rafaelsen Mania Scale; C: Control; CMNF: Crisis management with naturalistic follow-up; DAS: Disability assessment scale; DASS-21: Depression, Anxiety, Stress Scale; FES: Family Environment Scale (Cohesion, Expressiveness e Conflict)-Relationship subscales; FFT: Program of pharmacotherapy and family-focused

psychoeducational treatment; GAF: Global Assessment of Functioning; GHQ12: General Health Questionnaire 12; GCPBD: Guide for Caregivers of People with Bipolar Disorder; HAM–D: Hamilton Rating Scale for Depression–17-item; IEQ: Involvement evaluation questionnaire; IFT: Individual family therapy; IPP: Inventory of psychosocial problems; IPSQ: Interactional Problem Solving Questionnaire; KBDS: Knowledge of Bipolar Disorder Scale; KPI: Interactional coding system-assessed verbal and nonverbal communication behaviors of patients and their family; MFGP: Multifamily Group Psychoeducation; N: Total number l; ND: Not described; P: Psychoeducation; PFI: Psychoeducational family intervention; SADS-C: Schedule for Affective Disorders and Schizophrenia-Change Version; SCL-90: Symptom Checklist; SFGP: Solution Focused Group Psychotherapy; GT: Group therapy; WHOQOL Brief: World Health Organization Quality of Life, Brief version; WI: Without intervention; WL: Waiting list; YMRS: Young Mania Rating Scale.

to the perception of professional support received and help in times of emergency[51].

Two studies compared multifamily group psychoeducation, individual family therapy (IFT), and solution focused group psychotherapy (SFGP)[52,54]. There were no differences between these strategies regarding reduction in frequency of mood episodes[53,56], quality of life[52], or changes in functional status[53,54]. One study found that parents submitted to IFT reduced the incidence of hospital admissions[54].

The Guide for Caregivers of People with BD[50] was not associated with changes in relatives' symptoms of anxiety, depression or mania; stress discharge; knowledge of the disease; or changes in the caregiver burden[50].

DISCUSSION

Psychoeducation applied to BD patients and their relatives is associated with a reduction in the frequency of new mood episodes and a reduction in the number of hospital admissions and LOS. Psychoeducational interventions applied to patients contribute to improvement in pharmacological treatment adherence. Psychoeducation does not seem to influence the severity of depressive or manic symptoms or functionality. PMBD was associated with a higher adherence to pharmacological treatment and a higher quality of life in one study[23]. Psychoeducation strategies applied to relatives had no effect on adherence to pharmacological treatment.

Psychoeducational strategies in patients with BD are associated with a lower frequency of mood swings. These results are in line with a previous meta-analysis that evaluated 650 patients; 45% did not present a new mood episode compared to 30% of controls[54]. A possible explanation for this association is that the occurrence of subsyndromal symptoms is one of the main risk factors for new episodes[57,58]. Psychoeducational strategies in patients promote increased understanding about their own disease[59], improve the abilities of recognizing mood subsyndromal symptoms, enable early interventions, and might contribute to refraining new mood episodes[60]. Psychoeducational strategies also provide information about healthier lifestyles, sleep routines, exercise and stress management tips. All these steps are important to the maintenance of the euthymic state in BD[59].

Psychoeducation interventions were effective in reducing the frequency of hospitalizations and LOS and enhanced adherence to pharmacological treatment. Knowledge regarding their own illness might enrich comprehension of the importance of medication use and its effects on mood[61]. Moreover, a higher adherence to treatment is associated with monotherapy and reduced drug side effects[4,62]. Psychoeducational approaches to family members had no influence on treatment adherence.

When applied to patients and family members, psychoeducational approaches did not have an effect on mood severity symptoms, functionality or the quality of life of BD patients. Mood changes might lead to social, interpersonal and occupational impairments and contribute negatively to quality of life[63,64]. Depressive episodes are the most common and the most persistent affective states in BD and are the main cause of functional disability[4]. Residual and persistent depressive symptoms, cognitive decline, sleep deprivation, past history of psychotic symptoms[65,66], current presence of psychiatric comorbidities, use of psychoactive substances[65-68], long course of the disease, number of mood episodes[69-71], and hospitalizations[72] are associated with a reduction in functionality[73].

Family member psychoeducation is related to a lower frequency of mood swings and to a reduction in LOS. As family members acquire knowledge of the disease, they become more able to help patients identify early mood changes, apply assertive strategies to deal with daily situations and crisis management[48,74]. Through the provision of care, acceptance of the disease and dialogue, family members present themselves to the patient as a source of aid and support for decisions about their treatment[75-77].

In regard to the limitations of the present study, we might consider meta-analysis to be unable to be performed, owing to the methodological differences between heterogeneous studies (sample size, duration of follow-up, main results, type of comparison group), the population characteristics (severity, comorbidity, clinical status of patients in recruiting phase) and the intervention itself (target population, format, content, duration). All of these factors hamper the generalization of the results. In addition, the findings of the present study reveal that the characteristics of the sampling must be carefully considered. Patients with severe chronic disease may have poorer treatment responses. Future research to clarify the effectiveness of psychoeducation and to identify the determinants of response to treatment might be required for this population.

CONCLUSION

The data from this systematic review show the positive effects of the psychoeducational intervention on both patients and family members. Despite the lack of effectiveness in some parameters, psychoeducation has been associated with other treatments as an additional intervention. It is recommended that additional studies should approach strategies that aim to maximize the benefits of those therapies, adding interventions focused on family and interpersonal relationships.

ARTICLE HIGHLIGHTS

Research background

The bipolar disorder (BD) treatment is challenging, and there is some evidence that non-pharmacological interventions promote effects in the treatment of acute mood episodes and maintenance treatment. Psychoeducation is an intervention strategy based on providing patients and/or relatives with information about the disorder to enhance their understanding and enable early identification of warning signs and mood changes, improving treatment adherence, and have showed some results in order to help the BD treatments.

Research motivation

Even using adequate drug strategies, BD is characterized by high rates of occurrence of mood episodes, number of hospital admissions, and a progressive impairment. We aimed to summarize the best evidence of psychoeducation in the treatment of BD, considering patients and their family members.

Research objectives

This systematic review aims to investigate the role of psychoeducation in BD in patients and in their family members.

Research methods

A systematic search of original studies on psychoeducation with patients with Bipolar Affective Disorder and their families was carried out using Medline, Scopus and Lilacs databases. A data extraction table was created based on the Cochrane model and the methodological quality of the studies was assessed according to the criteria of the Newcastle-Ottawa scale.

Research results

Psychoeducation applied to BD patients and their relatives is associated with a reduction in the frequency of new mood episodes and a reduction in the number of hospital admissions and length of stay. Psychoeducational interventions applied to patients contribute to improvement in pharmacological treatment adherence, although the same effect it is not observed when applied to relatives. Psychoeducation does not seem to influence the severity of depressive or manic symptoms or functionality.

Research conclusions

Psychoeducation as an adjunct strategy to pharmacotherapy has been shown to be effective in the treatment of Bipolar Affective Disorder.

Research perspectives

To systematize the effectiveness of psychoeducation intervention on BD patients and family members.

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