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ORIGINAL ARTICLE

Observational Study

Validity, reliability, and psychometric properties of a computerized, cognitive assessment test (Cognivue®)

Diego Cahn-Hidalgo, Paul W Estes, Reina Benabou

ORCID number: Diego Cahn-Hidalgo (0000-0003-4529-0470); Paul W Estes (0000-0002-0018-2284); Reina Benabou (0000-0002-1935-8470).

Author contributions: Cahn-Hidalgo D drafted the initial manuscript; Estes PW and Benabou R performed data analysis for this research; and all three authors reviewed and revised the initial draft, and subsequently reviewed and approved the final, submitted manuscript.

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Conflict-of-interest statement: Dr. Cahn-Hidalgo has acted as a consultant and speaker for Cognivue Inc. Estes PW and Dr. Benabou are employees of Cognivue Inc.

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Diego Cahn-Hidalgo, Internal Medicine of Brighton, Rochester, NY 14623, United States

Paul W Estes, Reina Benabou, Cognivue Inc., Victor, NY 14564, United States

Corresponding author: Reina Benabou, MD, PhD, Cognivue Inc., 7911 Rae Blvd, Victor, NY 14564, United States. rbenabou@cognivue.com

Abstract

BACKGROUND

Cognitive issues such as Alzheimer's disease and other dementias confer a substantial negative impact. Problems relating to sensitivity, subjectivity, and inherent bias can limit the usefulness of many traditional methods of assessing cognitive impairment.

AIM

To determine cut-off scores for classification of cognitive impairment, and assess Cognivue® safety and efficacy in a large validation study.

METHODS

Adults (age 55-95 years) at risk for age-related cognitive decline or dementia were invited *via* posters and email to participate in two cohort studies conducted at various outpatient clinics and assisted- and independent-living facilities. In the cut-off score determination study (n = 92), optimization analyses by positive percent agreement (PPA) and negative percent agreement (NPA), and by accuracy and error bias were conducted. In the clinical validation study (n = 401), regression, rank linear regression, and factor analyses were conducted. Participants in the clinical validation study also completed other neuropsychological tests.

RESULTS

For the cut-off score determination study, 92 participants completed St. Louis University Mental Status (SLUMS, reference standard) and Cognivue® tests. Analyses showed that SLUMS cut-off scores of < 21 (impairment) and > 26 (no impairment) corresponded to Cognivue® scores of 54.5 (NPA = 0.92; PPA = 0.64) and 78.5 (NPA = 0.5; PPA = 0.79), respectively. Therefore, conservatively, Cognivue® scores of 55-64 corresponded to impairment, and 74-79 to no impairment. For the clinical validation study, 401 participants completed ≥ 1 testing session, and 358 completed 2 sessions 1-2 wk apart. Cognivue® classification scores were validated, demonstrating good agreement with SLUMS scores (weighted κ 0.57; 95%CI: 0.50-0.63). Reliability analyses showed similar

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scores across repeated testing for Cognivue® (R^2 = 0.81; r = 0.90) and SLUMS (R^2 = 0.67; r = 0.82). Psychometric validity of Cognivue® was demonstrated vs. traditional neuropsychological tests. Scores were most closely correlated with measures of verbal processing, manual dexterity/speed, visual contrast sensitivity, visuospatial/executive function, and speed/sequencing.

CONCLUSION
Cognivue® scores ≤ 50 avoid misclassification of impairment, and scores ≥ 75 avoid misclassification of unimpairment. The validation study demonstrates good agreement between Cognivue® and SLUMS; superior reliability; and good psychometric validity.

Key words: Cognitive screening test; Dementia; Memory; Motor control; Perceptual processing; Visual salience

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Core tip: This study was designed to address the question of how to identify early cognitive impairment and how to monitor cognitive impairment over time with high reliability. This is critical in patients at risk for age-related cognitive decline. The study results demonstrated that Cognivue - through its unique adaptive psychophysics technology - had good validity and psychometric properties, as well as superior test-retest reliability compared to the St. Louis University Mental Status examination. Therefore, as a quantitative, computerized, assessment tool, Cognivue represents a safe and effective method for clinicians to more conveniently and effectively identify and track cognitive impairment.

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INTRODUCTION

Tools for assessing cognitive function decline are often limited by issues of measurement efficacy[1-5], testing bias[5,6], inconsistent retest reliability[7], or cost[8]. In addition, some tests cannot be administered by non-clinicians, and excessive test length can make some tools impractical for routine use in clinical practice[6,9,10]. Cognivue® is a physiological and psychophysical computerized tool for the automated assessment of cognitive functioning that is not dependent on traditional question-and-answer testing. It was developed based on extensive basic research into the neural mechanisms of functional impairment in memory, aging, and dementia. This was complimented by clinical research demonstrating letter, word, and motion perceptual deficits in patients with Alzheimer's disease[11-14].

Cognivue® consists of 3 sub-batteries of 10 separately scored sub-tests presented in a 10 min automated sequence. The first sub-battery (visuomotor and visual salience) measures adaptive motor control and dynamic visual contrast sensitivity. These results do not count towards the final score. They are used only to adapt the remaining sub-tests to the response characteristics of the individual subject. This ensures that only cognition is evaluated, and the subject is not at a disadvantage because of visual or motor deficits. The subsequent 2 sub-batteries include perceptual processing (letter, word, shape, and motion discrimination), and memory processing (letter, word, shape, and motion memory). Cognivue® is Food and Drug Administration (FDA)-cleared for use as an adjunctive tool to aid in assessing cognitive impairment in subjects aged 55-95 years and is not intended to be used alone for diagnostic purposes.

This manuscript presents the full results of 2 clinical studies (previously presented at the 2019 annual meeting of the American Association of Geriatric Psychiatry) conducted to assess the efficacy and safety of Cognivue®. The purpose of the first study was to establish Cognivue® cut-off values (*e.g.*, impaired, intermediate, and

unimpaired cognitive function) compared to a reference standard, the St. Louis University Mental Status (SLUMS) Examination. The objective of the subsequent FDA pivotal trial was to clinically validate the agreement between the Cognivue® classifications and the SLUMS classifications, examine test-retest reliability, and determine the psychometric properties of the tests.

MATERIALS AND METHODS

Cut-off score determination study

The study to determine Cognivue® cut-off scores for the classification of cognitive impairment enrolled 92 adults 55 to 95 years of age from assisted and independent-living communities who were at risk for age-related cognitive decline or dementia. Subjects were invited via posters and email to complete both the SLUMS (reference standard) and Cognivue® tests. Exclusion criteria included the presence of motor or visual disabilities and the inability to provide informed consent.

The SLUMS is an 11-item questionnaire with scores ranging from 0 to 30, and it is designed to measure orientation, memory, attention, and executive functions. As previously described, the Cognivue® quantitative assessment tool includes 3 sequentially automated sub-batteries (visuomotor ability, perceptual processing, and memory processing) over a brief 10 min session (Table 1 and Figure 1). The first sub-battery is used to calibrate the subsequent tests based on the individual's visual and motor abilities. Participants in this study were stratified according to SLUMS score (> 26 = unimpaired, 26-21 = mildly impaired, and < 21 = impaired)[15].

Two different optimization methods were used to determine the cut-off values for Cognivue® scores that corresponded to the SLUMS classifications unimpaired, intermediate (mildly impaired), and impaired. The first method used a minimization algorithm to optimize the negative percent agreement (NPA) and positive percent agreement (PPA) between Cognivue® and SLUMS scores in the objective function: (1) NPA = [true negative (TN)/false positive (FP) + TN] × 100%; and (2) PPA = [true positive (TP)/false negative (FN) + TP] × 100%.

The second method used a minimization algorithm with two measures in the objective function, inaccuracy and error bias: (1) Inaccuracy = 1 - (TP + TN/total); (2) Error bias = contrast ratio (difference/sum) of FPs and FNs.

Clinical validation study

The validation study enrolled 401 adults 55 to 95 years of age at risk for age-related cognitive decline or dementia residing in independent-living communities who were invited via posters and email. Exclusion criteria included the presence of motor or visual disabilities and the inability to provide informed consent. Participants completed Cognivue®, SLUMS, and an array of traditional neuropsychological tests (Table 2). Results of the cut-off determination study were used to group the participants, with subjects in the intermediate categories (low to moderate impairment) being combined with the unimpaired category for each testing modality.

Agreement analysis of the impairment classifications as defined in the cut-off determination study was performed, along with an assessment of the retest reliability of Cognivue®, and a comparison of its psychometric properties relative to other neuropsychological tests (Table 2). Regression analyses for agreement and retest reliability, and rank linear regression and factor analysis for psychometric comparisons, among others were performed (Table 2).

RESULTS

Cut-off score determination study

A total of 92 participants completed both the SLUMS and the Cognivue® tests at one of five sites. Individual scores for study participants are shown in Figure 2. Based on SLUMS score, 50% were unimpaired (> 26), 38% were mildly impaired (26-21), and 12% were impaired (< 21) (Figure 2).

In the analysis of NPA and PPA, the SLUMS cut-off score for impaired (< 21) minimized to 0.297 at a Cognivue® cut-off score of 63.5 (NPA = 0.80; PPA = 0.79). The SLUMS cut-off score for unimpaired (> 26) minimized to 0.324 at a Cognivue® cut-off score of 73.5 (NPA = 0.68; PPA = 0.67). In the analysis of optimization by accuracy and error bias, the SLUMS cut-off score of < 21 (impaired) corresponded to a Cognivue® cut-off score of 54.5 (NPA = 0.92; PPA = 0.64). The SLUMS cut-off score of > 26 (unimpaired) corresponded to a Cognivue® cut-off score of 78.5 (NPA = 0.5; PPA = 0.79).

Table 1 Components of the Cognivue® quantitative assessment tool

Sub-battery and Sub-test	Description
Basic motor and visual ability	
Adaptive motor control test	Assesses visuomotor responsiveness using speed and accuracy measures
	Measures subject's ability to control the rotatory movement of the CogniWheel™ in response to rotational visual stimuli
Visual salience test	Assesses basic visual processing functions
	Measures the subject's ability to identify a wedge filled by a random pattern of black and white dots shown on an neutral (gray) background
Perceptual processing	
Letter discrimination	Measures the subject's perceptual processing of different forms, despite the addition of increasing amounts of clutter
	Discriminate real English letters from a variety of non-letter, letter-like shapes
Word discrimination	As above
	Discriminate real 3-letter words from 3-letter non-words
Shape discrimination	As above
	Discriminate a circle filled with a common shape from the rest of the display filled with other common shapes
Motion discrimination	As above
	Discriminate a circle filled with one direction of dot motion from the rest of the display filled with another direction of dot motion
Memory processing	
Letter memory	Assesses memory using specialized sets of visual stimuli
	Measures the subject's ability to recall which letter was presented as a pre-cue, and then select that letter from a display of alternative items, despite the addition of increasing amounts of clutter
	Select the correct letter of the English alphabet
Word memory	As above
	Select the correct 3-letter word
Shape memory	As above
	Select the correct shape
Motion memory	As above
	Select the correct direction of motion

Based on the 2 separate analysis techniques, it was determined that Cognivue® scores between 55 and 64 corresponded to SLUMS scores indicating impaired (0 to 20), and Cognivue® scores between 74 and 79 corresponded to SLUMS scores indicating unimpaired (27 to 30). Cognivue® scores between the ranges classifying impaired and unimpaired (64 and 74) corresponded to SLUMS scores of 21 to 26. Therefore, Cognivue® scores ≤ 50 provide a conservative standard consistent with cognitive impairment that will avoid misclassification of an individual that is impaired, and scores ≥ 75 provide a conservative cut-off consistent with no impairment that will avoid misclassification of an individual that is unimpaired (Table 3).

Clinical validation study

Part 1: Validation analyses: A total of 401 participants completed at least 1 testing session, and based on SLUMS score, 30% were unimpaired (> 26), 43% were mildly impaired (26-21), and 27% were impaired (< 21). Validation analysis of the previously defined Cognivue® classification scores yielded a PPA of 56% [95% Wilson interval (WI), 0.47-0.65] and a NPA of 95% (95%WI, 0.91-0.97), with a weighted $\kappa = 0.57$ [95% confidence intervals (CI): 0.50-0.63]. This suggests a significant categorical relationship between Cognivue® and SLUMS scores. An analysis omitting the intermediate groups as being indeterminate showed a stronger relationship between Cognivue® and SLUMS categories for impaired or unimpaired, with a PPA of 82% (95%WI, 0.72-0.89) and a NPA of 98% (95%WI, 0.93-0.99).

Part 2: Retest reliability analyses: Data were available for 358 participants who completed 2 Cognivue® testing sessions, 1-2 wk apart. Regression analyses of test-retest reliability produced similar scores across repeat testing for Cognivue®

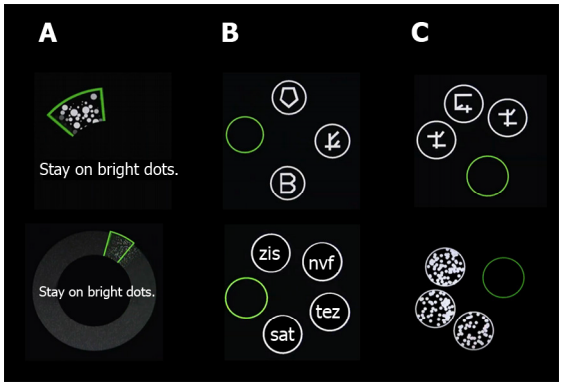


Figure 1 Cognivue® quantitative sub-batteries. A: Visuomotor testing (motor control, visual salience); B: Perceptual processing (letter, word, shape, motion); C: Memory testing (letter, word, shape, motion).

(regression fit: R^2 = 0.81; r = 0.90) (Figure 3A) and SLUMS (regression fit: R^2 = 0.67; r = 0.82) (Figure 3B).

Agreement analysis for Cognivue® test-retest reliability revealed strong correlation between participant classification by first and second Cognivue® tests (PPA = 89%; NPA = 93%), with an intraclass correlation (ICC) of tests 1 and 2 of 0.99 (P < 0.001). The agreement analysis for SLUMS also showed strong agreement between participant classification by first and second SLUMS tests (PPA = 87%; NPA = 87%; ICC, 0.87; P < 0.001).

The Cognivue® classifications of impaired, intermediate, and unimpaired did not differ significantly across repeat testing. Analyzing the 3 classifications separately yielded PPAs of 89% for impaired, 57% for intermediate, and 87% for unimpaired (Table 4). Whereas for SLUMS, the relationships between scores and classifications across repeated testing were less robust than those for Cognivue®. Analyzing the 3 SLUMS classifications separately yielded PPAs of 87% for impaired, 55% for mildly impaired, and 51% for unimpaired.

Psychometric analysis: This analysis was based on data from the 401 participants who had completed at least one testing session which included Cognivue®, SLUMS, and a battery of other traditional neuropsychological tests. Rank scores on each psychometric test were plotted against their ranks on SLUMS scores and against their ranks on Cognivue® scores with linear regression lines, the lines' parameters, and their 95% confidence intervals.

Data were then condensed using a factor analysis of the various neuropsychological test scores. Tests were grouped according to relations between scores across participants. The factor analysis converged in six iterations to yield a five factor solution showing Cognivue® scores most closely correlated with the following types of measures: verbal processing (animal naming and Rey Auditory Verbal Learning Test), manual dexterity and speed (Peg Board), visual acuity (contrast sensitivity), visuospatial and executive function (Trail Making Test-B and judgment of line orientation), and speed and sequencing (Trail Making Test-A) (Table 5).

The five factor scores for each participant were used in a multiple linear regression analyses for Cognivue® scores and yielded an adjusted linear R^2 of 0.67 (Figure 4A). Similar analysis for SLUMS scores yielded an adjusted linear R^2 of 0.65 (Figure 4B).

DISCUSSION

In the US, estimates of the prevalence of mild cognitive impairment range from 15%-20% among those ≥ 65 years of age[16], and 9.9%-35.2% among those ≥ 70 years of age[17-19], representing a substantial potential impact on both direct and indirect costs. Studies show cognitive issues such as Alzheimer's disease and other dementias confer substantial negative impacts, including increased hospitalization, assisted living stays, home health care visits, risk of in hospital mortality, as well as increased costs compared to those without such impairments[16].

Cognivue® was designed to overcome some of the limitations inherent in traditional paper and pencil tests for assessing cognitive impairment, such as sensitivity[1,2], subjectivity[3], test-retest reliability[7], as well as educational, language, gender, and cultural biases[5,6].

Table 2 Summary of the purpose and analyses of the components of the Food and Drug Administration pivotal clinical trial of Cognivue®

Validation of classification scores	Purpose: Assess the validity of the previously defined Cognivue® cut-off scores in a larger sample of subjects
	Methods: Scores on Cognivue® and SLUMS were compared using regression and classification analyses. PPA and NPA were calculated
Assessment of retest reliability	Purpose: Compare scores from repeated administration of Cognivue® to assess retest reliability, compare findings to parallel results from SLUMS
	Methods: Repeated Cognivue® and SLUMS testing was conducted in 2 sessions 1-2 wk apart with regression and rank linear regression analysis being performed
Assessment of score psychometrics *vs* other neuropsychological tests	Purpose: Compare scores on Cognivue® and other neuropsychological tests to describe relationship and compare them to SLUMS
	Methods: 401 participants completed 10 different tests [SLUMS, SLUMS-clock drawing[1], SLUMS-animal naming[1], RAVLT, TMT-A, TMT-B, Benton JOLO, figural memory, PPB, HVCS, GDS (15-item)]; rank linear regression analysis and factor analysis performed

[1]Scored separately from overall St. Louis University Mental Status. GDS: Geriatric Depression Scale; HVCS: Hamilton-Veale Contrast Sensitivity; JOLO: Judgment of line orientation; NPA: Negative percent agreement; PPA: Positive percent agreement; PPB: Purdue Peg Board; RAVLT: Rey Auditory Verbal Learning Test; SLUMS: St. Louis University Mental Status; TMT-A: Trail Making Test-A; TMT-B: Trail Making Test-B.

Cognivue® eliminates these biases through its unique adaptive psychophysics technology, which focuses on whether the subject can detect and identify stimuli, including differentiating between different stimuli, and describing the magnitude or nature of the difference. This is unrelated to the subject's level of education or social/economic status. Furthermore, the first sub-battery of tests is designed to assess the individual's visual and motor abilities. These are used only to adapt subsequent tests, and therefore, eliminate bias related to visual and motor deficits and assessing only the individual's cognitive function.

The dynamic, adaptive technology avoids memorization issues associated with current paper and pencil tests. The test-retest results of this trial suggest that Cognivue® may help eliminate or reduce the effect of memorization and human error/variability on retest reliability[7], while the retests with SLUMS showed a lower degree of retest reliability. Cognivue® subjects are unable to memorize answers due to the adaptive nature of the test.

Other barriers to cognitive testing in clinical practice include the impact on costs and scheduling flexibility that are related to the need for administration by the provider specifically[6,9,20]. Cognivue® is self-administered by the patient and can be initiated by non-clinician support staff. Work load is also reduced by the ability of Cognivue® to track and monitor test outcomes over repeat testing over time.

In a survey of primary care providers, diagnosis and treatment of mild cognitive impairment was impacted by a negative attitude toward the importance of early diagnosis[21]. Recent recommendations recognized that cognitive impairment occurs on a continuum, progressing from age-related decline, to mild cognitive impairment, and to dementia[22]. Early identification of cognitive impairment can lead to earlier management, which can lead to improved prognosis and decreased morbidity, and early discussion regarding decision-making[23,24]. In fact, patients often identify assistance in planning for future treatments as a factor influencing their willingness to be screened[22]. In clinical practice, physician clinical judgment is less effective than structured tools for the recognition of mild cognitive impairment[25]. The 2017 Geriatric Summit on Assessing Cognitive Disorders Among the Aging Population sponsored by the National Academy of Neuropsychology, emphasized the importance of ongoing screening, and the need for automated tools for assessing and recording patient's results over time[26]. Cognivue®, provides an easy-to-use reliable, computerized, testing tool, which can help clinicians meet these needs.

A limitation of the present studies validating Cognivue® is the use of a single reference standard, SLUMS. However, although Cognivue® has not yet been compared to Mini-Mental Status Examination (MMSE) or Montreal Cognitive Assessment (MoCA) tests—two of the more widely used paper and pencil cognitive assessments—SLUMS has been[15,27-29]. These studies demonstrated either the equivalence or superiority of SLUMS. Therefore, it is a reasonable to infer the likely equivalence, at a minimum, of Cognivue® in terms of its sensitivity, specificity, and psychometric validity to these commonly used tools. Cognivue® may be less likely to under diagnose (reported with MMSE)[28], or over diagnosis mild cases of impairment (10% with MMSE, 25% with MoCA)[22].

Longitudinal follow-up studies are underway to assess the ability of Cognivue® to

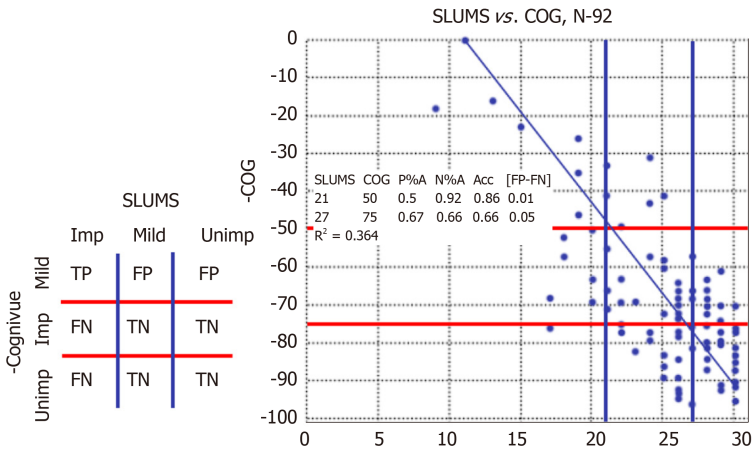


Figure 2 Scatterplot showing the St Louis University Mental Status and Cognivue® scores for the 92 study participants. The table to the left of the scatter plot provides a key for relating the plot to participant classifications. Above the upper horizontal red line shows Cognivue® scores of < 50 and to the left of the left vertical blue line shows St. Louis University Mental Status (SLUMS) scores < 21 denoting impaired. Below the bottom horizontal red line shows Cognivue® scores of > 75 and to the right of the right vertical blue line shows SLUMS > 27 denoting unimpaired. Results of the analyses of classification are included in the table enclosed in the scatter plot. ACC: Accuracy; FN: False negative; FP: False positive; N%A: Negative percent agreement; P%A: Positive percent agreement; SLUMS: St. Louis University Mental Status; TN: True negative; TP: True positive.

monitor cognitive deterioration over time. Cognivue® is also being studied in other patient populations and specific disease states such as multiple sclerosis[30]. Additionally, a highly portable model of Cognivue® with a Health Insurance Portability and Accountability Act-compliant data repository is scheduled to be launched in mid-2019.

In conclusion, Cognivue® scores ≤ 50 and ≥ 75 were consistent with conservative standards for impaired and unimpaired, respectively, in the cut-off study. When these scores were used in the clinical trial also reported here, Cognivue® was shown to have good validity and psychometric properties, and superior test- retest reliability compared to SLUMS. As a result, Cognivue® received FDA de novo 510(k) clearance as an adjunctive tool for evaluating cognition through perceptual and memory function in individuals 55-95 years of age[31]. It is not intended to be used as a diagnostic tool.

These studies demonstrated the safety and efficacy of Cognivue®, which is the first FDA-cleared test for the automated computerized assessment of cognitive functioning. This represents an improved approach to help in the early identification of cognitive impairment in patients at-risk for cognitive decline.

Table 3 Summary of Cognivue® cut-off score analysis

	SLUMS cut-off scores		Cognivue® cut-off scores
Impaired	< 21	→	≤ 50
Mildly impaired (intermediate)	21-26	→	51-74
Unimpaired	> 26	→	≥ 75

SLUMS: St. Louis University Mental Status.

Table 4 Proportion of participants classified in each impairment category by first and second Cognivue® tests

2nd Test	1st Test			
	Impaired	Intermediate	Unimpaired	Total
Impaired	42 (89%)	21	0	63
Intermediate	5	41 (57%)	32	78
Unimpaired	0	10	207 (87%)	217
Total	47	72	239	358

Table 5 Factor analysis component matrix for the neuropsychological test scores indicating correlations with Cognivue®

	Component				
	1	2	3	4	5
SLUMS-clock drawing	0.420	0.338	0.038	0.367	-0.049
SLUMS-animal naming	0.529[1]	0.346	0.146	0.365	-0.125
RAVLT-A-1	0.718[1]	0.209	0.034	0.128	-0.040
RAVLT-A-2	0.820[1]	0.204	0.080	0.157	-0.138
RAVLT-A-3	0.832[1]	0.193	0.120	0.190	-0.057
RAVLT-A-4	0.847[1]	0.200	0.143	0.184	-0.040
RAVLT-A-5	0.863[1]	0.210	0.080	0.182	-0.013
RAVLT-B-1	0.579[1]	0.213	0.104	0.178	-0.060
RAVLT-A-6	0.852[1]	0.134	0.093	0.170	-0.051
RAVLT-A-7	0.860[1]	0.159	0.117	0.164	-0.040
RAVLT-hits	0.670[1]	0.052	0.128	0.252	-0.003
RAVLT-fps	-0.408	-0.017	-.111	-0.041	0.125
Peg Board-Left	0.247	0.796[2]	0.297	0.120	-0.090
Peg Board-Right	0.297	0.752[2]	0.206	0.160	-0.186
Peg Board-Bimanual	0.293	0.822[2]	0.230	0.134	-0.137
Contrast-Left	0.146	0.133	0.801[3]	0.110	-0.068
Contrast-Right	0.160	0.156	0.802[3]	0.094	-0.106
Contrast-Binocular	0.189	0.183	0.833[3]	0.132	-0.153
TMT-B-Time	-0.312	-0.088	-0.213	-0.788[4]	0.116
TMT-B-Errors	-0.266	-0.072	-0.197	-0.815[4]	0.085
Benton JOLO	0.185	0.196	-0.024	0.499[4]	-0.344
TMT-A-Time	-0.115	-0.185	-0.158	-0.150	0.862[5]
TMT-A-Errors	-0.081	-0.058	-0.134	-0.068	0.902[5]
Figural memory	0.272	0.243	0.202	0.376	0.047
GDS	-0.119	-0.341	0.207	-0.329	-0.008

[1]Cognivue® scores most closely correlated with verbal processing (animal naming and Rey Auditory Verbal Learning Test);
[2]Cognivue® scores most closely correlated with manual dexterity and speed (Peg Board);
[3]Cognivue® scores most closely correlated with visual acuity (contrast sensitivity);
[4]Cognivue® scores most closely correlated with visuospatial and executive function (Trails B and judgment of line orientation);
[5]Cognivue® scores most closely correlated with speed and sequencing (Trails A). Fps: Frames per second; GDS: Geriatric Depression Scale; JOLO: Judgment of line orientation; RAVLT: Rey Auditory Verbal Learning Test; SLUMS: St. Louis University Mental Status; TMT: Trail Making Test.

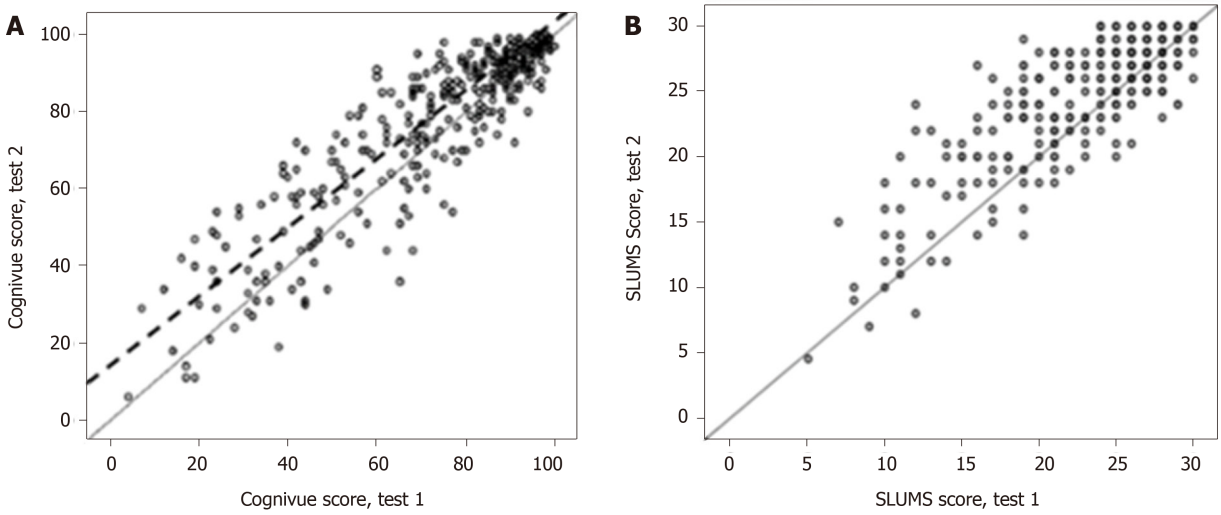


Figure 3 Scatterplot showing first test scores (abscissa) and second test scores (ordinate) co-plotted with a Deming regression line (dashed) and 45° line (solid) for Cognivue® and the St Louis University Mental Status. A: Cognivue®; B: St. Louis University Mental Status. Cognivue®: Intercept of line: 95% confidence interval (CI): 4.27-13.84 (SE = 2.433; *P* = 0.0002); slope of line: 95%CI: 0.880-0.993 (SE = 0.0285; *P* = 0.0264); regression fit: R^2 = 0.81 (*r* = 0.90). St. Louis University Mental Status: Intercept of line: 95%CI: 2.24-6.06 (SE = 0.970; *P* < 0.0001); slope of line: 95%CI: 0.82-0.97 (SE = 0.039; *P* = 0.039); regression fit: R^2 = 0.67 (*r* = 0.82). SLUMS: St. Louis University Mental Status.

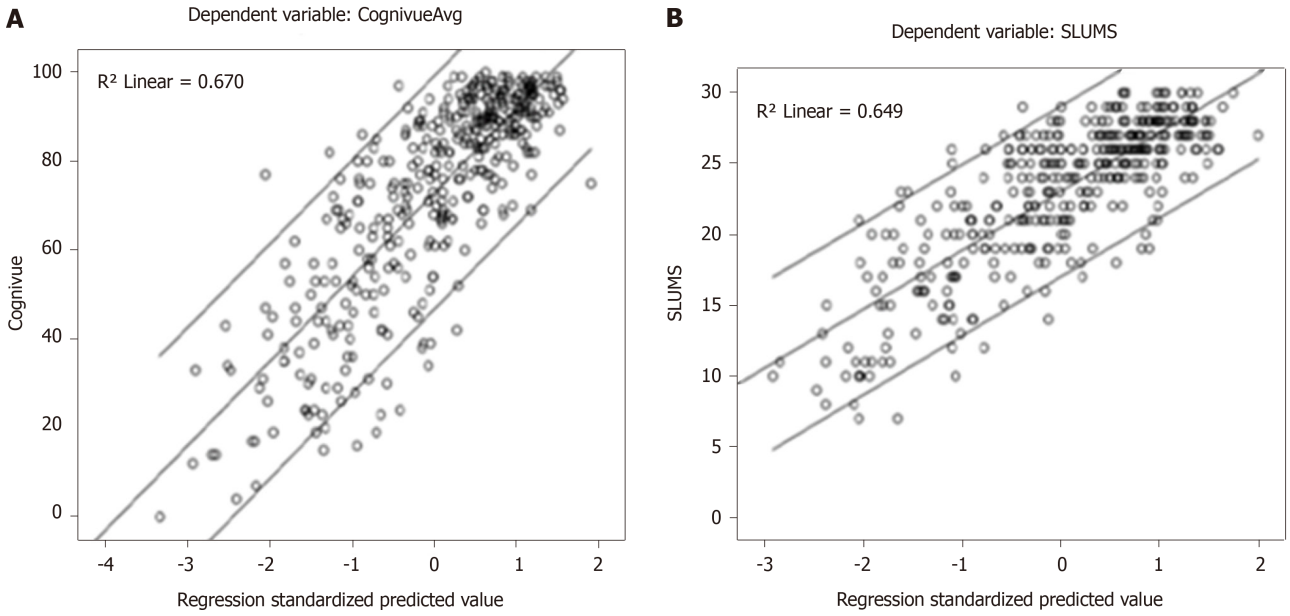


Figure 4 Scatterplot showing regression standardized predicted values including all five factors and Cognivue® scores or the St Louis University Mental Status scores co-plotted with linear regression lines. A: Cognivue®; B: St. Louis University Mental Status. Avg: Average; R^2: Coefficient of determination; SLUMS: St. Louis University Mental Status.

ARTICLE HIGHLIGHTS

Research background

The assessment of declining cognitive function due to age or dementia is often impeded by multiple factors such as testing bias, cost, poor measurement efficacy, test inconsistency, and test length. Some tools also specifically require administration by a clinician, adding further constraint to routine testing in clinical practice. Prior research on the neural mechanisms of functional impairment in memory, aging, and dementia has led to the development of a novel computerized testing method.

Research motivation

There is a need for a reliable, easy-to-use, novel method for the early identification, testing, and monitoring of cognitive impairment in at-risk patient populations. Cognivue® is a safe and

effective automated method for identifying and tracking cognitive impairment in a more convenient and efficient manner than traditional question and answer paper and pencil testing.

Research objectives
The main objective of the first clinical study was to establish cut-off values for Cognivue® (*e.g.*, impaired, intermediate, and unimpaired cognitive function) relative to the St. Louis University Mental Status (SLUMS). The main objectives of the second study were to clinically validate the agreement between Cognivue® and SLUMS classifications, assess retest reliability of Cognivue®, and assess Cognivue®'s psychometric properties.

Research methods
Participants in the first study completed both the SLUMS and Cognivue® tests. Optimization methods used to determine cut-off values included a minimization algorithm to optimize the negative percent agreement and positive percent agreement between test scores in the objective function and a minimization algorithm with two measures in the objective function (inaccuracy, error bias). Participants in the second study also completed both the SLUMS and Cognivue® tests as well as other traditional neuropsychological tests. Regression analyses of agreement and retest reliability, as well as rank linear regression and factor analysis for psychometric comparisons were conducted, and agreement analysis of the impairment classifications derived from the first study was also performed.

Research results
It was found that Cognivue® scores ≤ 50 would avoid misclassification of an impaired person while providing a conservative standard consistent with cognitive impairment, and that scores ≥ 75 would avoid misclassification of an unimpaired person while providing a conservative cut-off consistent with no impairment. In the second study, Cognivue® demonstrated good validity and psychometric properties, as well as superior test-retest reliability compared to the SLUMS.

Research conclusions
With its unique adaptive psychophysics technology, Cognivue® provides a computerized tool for the automated assessment of cognitive functioning free from many of the biases and limitations of the more traditional paper and pencil methods such as sensitivity, subjectivity, test-retest reliability, and educational, language, gender, and cultural biases. Improved prognosis and decreased morbidity may be possible with an earlier implementation of management strategies in patients with cognitive impairment identified earlier in its course. Because Cognivue® is self-administered it provides clinicians with a safe, effective, and time-saving method to efficiently assist in the assessment and monitoring of cognitive impairment in their patients.

Research perspectives
Trials assessing the utility of Cognivue® in other, specific patient populations are currently in progress. Additionally, the ability of Cognivue® to monitor the deterioration of cognitive function over time is currently being assessed in longitudinal studies.

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REVIEW

Review of source-monitoring processes in obsessive-compulsive disorder

Layla Lavallé, Jérome Brunelin, Rémy Bation, Marine Mondino

ORCID number: Layla Lavallé (0000-0001-8469-9506); Jérome Brunelin (0000-0001-5479-5628); Rémy Bation (0000-0003-1598-982X); Marine Mondino (0000-0003-3175-8503).

Author contributions: Lavallé L wrote the first draft of the manuscript; Lavallé L and Mondino M managed the systematic literature searches; Mondino M supervised the study; Brunelin J and Bation R critically revised the manuscript. All authors approved the final version of the manuscript.

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Layla Lavallé, Jérome Brunelin, Rémy Bation, Marine Mondino, French National Institute of Health and Medical Research U1028, Centre National de la Recherche Scientifique UMR5292, Lyon Neuroscience Research Center, Lyon 69000, France

Layla Lavallé, Jérome Brunelin, Rémy Bation, Marine Mondino, Lyon University, Lyon 69000, France

Layla Lavallé, Jérome Brunelin, Rémy Bation, Marine Mondino, Centre Hospitalier le Vinatier, Batiment 416, Bron 69678, France

Rémy Bation, Psychiatric Unit, Wertheimer Neurologic Hospital, Bron 69500, France

Corresponding author: Jérome Brunelin, MSc, PhD, Academic Fellow, Academic Research, Senior Researcher, Lyon Neuroscience Research Center, CH Le Vinatier, Université Claude Bernard Lyon, PSY-R2 team, Bron 69678, France. jerome.brunelin@ch-le-vinatier.fr

Abstract

Obsessive-compulsive disorder (OCD) is a severe mental illness characterized by persistent, intrusive and distressing obsessions and/or compulsions. Such symptoms have been conceptualized as resulting from a failure in source-monitoring processes, suggesting that patients with OCD fail to distinguish actions they perform from those they just imagine doing. In this study, we aimed to provide an updated and exhaustive review of the literature examining the relationship between source-monitoring and OCD. A systematic search in the literature through January 2019 allowed us to identify 13 relevant publications investigating source-monitoring abilities in patients with OCD or participants with subclinical compulsive symptoms. Most of the retrieved studies did not report any source-monitoring deficits in clinical and subclinical subjects compared with healthy volunteers. However, most of the studies reported that patients with OCD and subclinical subjects displayed reduced confidence in source-monitoring judgments or global cognitive confidence compared to controls. The present review highlighted some methodological and statistical limitations. Consequently, further studies are needed to explore source monitoring with regard to the subcategories of OCD symptoms (*i.e.*, symmetry-ordering, contamination-washing, hoarding, aggressive obsession-checking, sexual-religious thoughts) and to clarify the relationship between source-monitoring subtypes (*i.e.*, reality or internal source-monitoring) and confidence in these populations.

Key words: Reality-monitoring; Source-monitoring; Obsessive-compulsive disorder;

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Subclinical compulsive symptoms

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Core tip: Symptoms of obsessive-compulsive disorder (OCD) have been proposed as resulting from a source-monitoring failure, suggesting that patients with OCD fail to distinguish actions they perform from those they just imagine doing. This study provides an updated and exhaustive review of the literature examining the relationship between source-monitoring performances and OCD. Most of the 13 retrieved studies did not report any source-monitoring deficits but reported reduced confidence in source-monitoring judgments in patients with OCD and subclinical subjects compared to controls. Furthermore, this review highlighted some methodological limitations and provided recommendations with respect to future studies focusing on source-monitoring in OCD.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a frequent psychiatric condition that occurs in 2%-3% of the population[1]. Symptoms consist of persistent, intrusive and distressing obsessions and/or compulsions, strongly impacting the quality of life of the affected individual[2]. Five dimensions of symptoms have been classically defined in patients with OCD: Symmetry-ordering, contamination-washing, hoarding, aggressive obsession-checking, and sexual-religious thoughts[3-7].

The pathophysiological and cognitive mechanisms underlying the symptoms of OCD have not yet been fully elucidated. However, several nonmutually exclusive cognitive models have been proposed to characterize OCD thought processes. For instance, according to the thought-action fusion model[8], excessive importance is given to patients' thoughts by believing that having a thought about an event makes that event more likely to occur. A second model, the meta-memory model[9], proposes that an imbalance between a preserved feeling of remembering (knowing) and an impaired ability to remember physical details (remembering) leads to checking behavior to restore an adequate level of confidence. A third cognitive model proposes that patients with OCD have source-monitoring disabilities[10]. Source-monitoring is defined as the ability to discriminate the origin of a remembered piece of information[11]. According to this model, patients with OCD would be more likely to confound memories of performed and imagined actions. The resulting uncertainty could therefore contribute to obsessive thoughts that in turn lead to compulsive behaviors to ensure that the intended actions have been carried out.

Three types of source-monitoring processes have been described in the literature[12]. The first type is reality-monitoring, which characterizes the ability to distinguish whether information was perceived from the environment or imagined (*e.g.*, Did I see my partner turn off the gas or did I only imagine it?). A second type of source monitoring is internal source monitoring, which characterizes the ability to determine whether an internally generated event was expressed in the external space or kept in the internal space (*e.g.*, Did I turn off the gas or did I only think about doing it?). Finally, external source monitoring refers to the discrimination between different externally derived sources (*e.g.*, Did John tell me this information, or did I hear it on the radio?). Deficits in source-monitoring processes have already been associated with some clinical features, such as delusions and hallucinations in schizophrenia. Namely, an incorrect flagging of thoughts as self-generated events may be responsible for altered self-recognition in patients with psychosis. In addition, their propensity to misattribute inner speech to external sources has been associated with the presence of auditory verbal hallucinations[13,14].

Here, we aimed to provide an updated overview of the literature examining the relationship between source-monitoring performances and OCD symptoms. Special attention was given to internal source monitoring since its alteration (*i.e.*, a confusion

between imagined and performed events) seems more related to OCD symptoms than reality-or external source monitoring. Finally, rather than only exploring source monitoring as an OCD trait, this review included both patients with OCD and subjects with subclinical checking rituals (defined as persons with similar checking symptoms as those observed in clinical subjects but with less-disabling consequences[15]). This will allow us to explore the relationship between source-monitoring deficits and OCD's related checking symptoms.

To achieve our goal, a systematic review was conducted according to the recommendations from the Cochrane group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[16]. Details of methods are given in the Supplementary material 1[17,18]. The primary electronic search in the PubMed, ScienceDirect and psycINFO databases identified 102 articles, and cross-referencing provided 6 additional articles. Removal of duplicate records yielded 100 articles. After reading the titles and abstracts, 24 articles were retained. Eleven records were excluded because they did not use source-monitoring tasks. This process resulted in a total of 13 full-text articles, comprising 10 studies in patients with OCD and 3 studies in a subclinical population of checkers. Main results and methods from the 13 selected studies investigating source-monitoring in patients with OCD and subjects with subclinical checking rituals are given in the Table 1[10,15,19-28].

INTERNAL SOURCE-MONITORING IN OBSESSIVE-COMPULSIVE DISORDER

Our systematic review yielded 9 studies that investigated internal source-monitoring abilities. These studies included either patients with OCD or subclinical checking-prone individuals. Among them, 2 studies reported that participants had significantly impaired internal source-monitoring abilities. These 2 studies compared participants with checking symptoms, either clinical (OCD checkers) or subclinical (checking-prone individuals). For instance, Rubenstein *et al*[15] compared the internal source-monitoring abilities between checking-prone individuals and healthy controls. They used a word-recognition task requiring participants to either read the second word of a pair of words or to generate the second word from its first letters. Participants were then asked to recognize whether the words were generated in the internal space or the external space (read aloud). The authors reported that checking-prone participants were more likely than healthy controls to misattribute read words as generated. Using a task measuring the participants' ability to remember if they actually performed, imagined themselves performing or imagined someone else performing some actions, Ecker *et al*[19] found a significant impairment in OCD checkers compared to low-checking inpatients with other diagnoses. Namely, OCD checkers had poorer free recall of performed actions and made more confusions between performed and imagined actions. Moreover, the authors reported that high-checking inpatients made significantly more misattributions of imagined events as being performed compared to low-checking ones.

In contrast to these studies, 7 other studies did not report any significant impairments regarding internal source-monitoring abilities. Among them, 4 studies included patients specifically suffering from checking symptoms, and 3 studies included patients with general OCD symptomatology. First, McNally *et al*[20], Zermatten *et al*[21], Constans *et al*[22], and Cougle *et al*[23] used action recognition tasks requiring participants to discriminate between actual and imagined action performance. They failed to report any significant difference between OCD checkers and noncheckers or healthy controls. Interestingly, Constans *et al*[22] and Cougle *et al*[23] used anxiety-eliciting actions. Using comparable action recognition tasks, Moritz *et al*[29] and Merckelbach *et al*[25] did not report any significant difference between patients with general OCD symptoms and healthy controls. They both divided their OCD groups into two subgroups, either high and low checkers[24] or checkers and noncheckers[25], but failed to find any significant difference between the subgroups. Finally, by including action items relevant to compulsive OCD behaviors, Hermans *et al*[24] also failed to reveal any significant difference between OCD patients and healthy controls.

OTHER SUBTYPES OF SOURCE MONITORING IN OBSESSIVE-COMPULSIVE DISORDER

Seven studies investigated other source-monitoring subtypes in patients with OCD or

Table 1 Details of studies investigating source monitoring in patients with obsessive-compulsive disorder or participants with subclinical compulsive symptoms

Ref.	SM subtype[1]	Samples (*n*)	SM task: Source encoding conditions	OCD relevant stimuli	Significant between-groups difference in SM performances	Significant between-groups difference in confidence
Hermans *et al*[24], 2003	Internal	17 OCD; 17 HC	ART: Imagining performing an action a fixed number of times + performing it a various number of times	Relevant compulsive + irrelevant compulsive + neutral actions	No difference between OCD and HC; No difference between high (n = 9) and low (n = 8) checkers	OCD < HC for neutral and irrelevant compulsive actions
Merckelbach *et al*[25], 2000	Internal	19 OCD; 16 HC	ART: Imagining performing *vs* performing actions	No	No difference between OCD and HC; No difference between OCD checkers (n = 7) and OCD noncheckers (n = 12)	OCD < HC. Negative correlation between DES scores and confidence in OCD but not in HC
Cougle *et al*[23], 2008	Internal	21 OCD checkers; 24 HC	ART: Imagining performing *vs* performing actions	Bothersome + nonbothersome actions	No difference between OCD checkers and HC in both free recall and recognition tests	OCD checkers < HC
Constans *et al*[22], 1995	Internal	12 OCD checkers; 7 HC	ART: Imagining performing *vs* performing actions within action sequences	Anxiety-eliciting + neutral objects	No difference between OCD checkers and HC	No difference
Ecker *et al*[19], 1995	Internal	24 OCD checkers; 24 HCIP + 48 LCIP	ART: Imagining performing *vs* performing *vs* imagining seeing *vs* subvocal rehearsal	Not specified	OCD < LCIP for free recall of performed actions and made more confusions between performed and imagined perform actions; HCIP: More misattributions of imagined actions as performed than LCIP	OCD checkers < HC, regardless of the instruction modality
McNally *et al*[20], 1993	Internal	12 OCD checkers; 12 OCD noncheckers; 12 HC	ART: Tracing *vs* imagining tracing *vs* seeing drawings or words	No	No difference between checkers and noncheckers	OCD noncheckers < HC for words or drawings they traced. OCD checkers and noncheckers < HC for words they imagined
Moritz *et al*[29], 2009	Internal	32 OCD; 32 HC	ART: Imagining *vs* performing actions	No	No difference between OCD and HC	No difference
	External	32 OCD; 32 HC	ART: Verbal *vs* nonverbal instruction (pictogram)		No difference between OCD and HC	
Rubenstein *et al*[15], 1993	Exp 1a: Internal + Reality	20 CP; 20 HC	ART: Seeing *vs* performing *vs* writing actions	No	CP made more SM confusions than HC	NA
	Exp 3: Internal	20 CP; 20 HC	WRT (word pair completion): Reading a word pair *vs* generating the second word of a pair	No	CP made more SM confusions than HC	NA

Zermatten *et al*[21], 2006	Internal + Reality	19 CP; 35 nonCP	ART: Imagining performing *vs* performing *vs* imagining seeing *vs* seeing *vs* verbally repeating	No	CP misattributed more performed actions as seen than nonCP (significant correlation with OCI-R checking); No difference for misattribution of performed actions as imagined perform	No difference
Reese *et al*[26], 2011	Reality	20 OCD; 20 HC; 20 BDD	WRT: Imagining seeing *vs* seeing words	Neutral + negative + BDD-related + OCD-related words	No difference between OCD and HC	No difference
Sher *et al*[10], 1983	Reality	26 CP; 28 nonCP	WRT (word pair completion): Imagining the second word of a pair *vs* seeing it written	No	No difference between CP and nonCP	CP < nonCP
Brown *et al*[27], 1994	Reality	28 OCD; 21 HC	WRT: Imagining seeing *vs* seeing words	No	OCD > HC. Among OCD, checkers (n = 13) < cleaners (n = 9)	NA
Kim *et al*[28], 2009	External	14 OCD; 14 HC	WRT: Female *vs* male voices	No	OCD < HC	Cognitive confidence subscores of MCQ were significantly higher in the OCD group than the control group; No correlation between confidence scores and SM

[1]Source-monitoring subtypes investigated in the selected studies were reclassified according to Source-Monitoring Framework as described in Johnson 1993. ART: Action recognition task; BDD: Body dysmorphic disorder; CP: Checking-prone subjects; DES: Dissociative Experience Scale; HC: Healthy controls; HCIP: High-checking inpatients; LCIP: Low-checking inpatients; NA: Not available; NS: Not significant; OCD: Obsessive-compulsive disorder; OCI-R: Obsessive-Compulsive Inventory- Revised; SM: Source monitoring; WRT: Word recognition task.

subclinical participants with checking symptoms.

Reality-monitoring

Among them, 4 studies measured reality-monitoring abilities in patients with OCD or subclinical participants with checking symptoms. Zermatten *et al*[21] used an action recognition task including four conditions: A condition in which subjects performed an action, a condition in which they imagined themselves performing the action, a condition in which they saw an action and a condition in which they imagined seeing the action. They found that checking-prone participants misattributed more performed actions as seen than nonchecking prone participants. The number of confusions between performed and seen actions significantly correlated with checking symptoms. Conversely, the 3 other studies did not reveal any significant reality-monitoring deficits. Using a word recognition task with items related or not related to OCD, Reese *et al*[26] did not find any impairments in patients with OCD compared to healthy controls. Surprisingly, Brown *et al*[27] reported that patients with OCD were significantly better than healthy controls in discriminating between words they saw and words they imagined. However, when the group of patients with OCD was split into two subgroups (cleaners and checkers), the authors reported that checkers were significantly impaired in reality monitoring compared to cleaners. Sher *et al*[10] did not observe any significant reality-monitoring impairments in subclinical checkers compared to noncheckers.

In addition, Rubenstein *et al*[15] compared source monitoring between checking-prone participants and healthy controls without distinguishing between internal source- and reality-monitoring abilities. They reported that checking-prone individuals made more confusions between actions they saw, performed or wrote, reflecting a general source-monitoring impairment.

External source-monitoring

Finally, 2 other studies compared external source-monitoring abilities between patients with OCD and healthy controls. Kim *et al*[28] found a significant external source-monitoring deficit in patients with OCD. Namely, patients with OCD showed a lower accuracy in recognizing whether words were presented with a male or female

voice compared to healthy controls. In contrast, Moritz *et al*[29] did not report any significant external source-monitoring impairment in patients with OCD compared to healthy controls.

CONFIDENCE IN OBSESSIVE-COMPULSIVE DISORDER

Among the 13 included studies, 11 investigated confidence in source-monitoring judgments in relation to OC symptoms. These studies evaluated either specific confidence in source-monitoring judgments[10,19-26,29] or global cognitive confidence using the Meta-Cognition Questionnaire[24,28]. A decrease in confidence in source-monitoring judgments was observed in studies including only checkers[10,19,20,23] and in those including patients with OCD without discriminating their clinical subtypes[24,25,28].

DISCUSSION

The aim of this review was to summarize the findings from studies investigating source-monitoring abilities in relation to OCD symptoms. The analysis of the literature did not lead to clear conclusions. Indeed, 5 of the 13 studies reviewed highlighted some differences in source-monitoring processes in patients with OCD or subclinical checkers compared to controls. Among them, two found reduced internal source-monitoring abilities in OCD checkers and checking-prone individuals (*i.e.*, confusions between imagined and performed items). One study found reduced reality-monitoring abilities between patients with OCD and healthy controls (*i.e.*, confusions between imagined and seen items). One study found reduced external source-monitoring in patients with OCD compared to healthy controls (*i.e.*, confusions between two external-source items). Finally, one study found that subclinical checkers displayed reduced general source-monitoring abilities than noncheckers. While only a few studies showed differences in source-monitoring performances, most of the studies reported that patients with OCD and checking-prone participants displayed reduced confidence compared to healthy controls.

Several methodological factors could have contributed to these discrepancies between findings. Indeed, we observed high methodological heterogeneity across studies, which limited the ability to make comparisons among studies. First, the current review highlighted disparities between studies regarding the definitions of the explored subtypes of source-monitoring (*i.e.*, reality-, internal source-, or external source-monitoring). To harmonize this, we reclassified the selected studies according to the definitions given by Johnson *et al*[12], where internal source monitoring refers to the distinction between two internal sources of information, reality monitoring refers to the distinction between internal and external sources, and external source monitoring refers to the distinction between two external sources. Thus, according to these definitions, some studies that announced the investigation of reality monitoring were reclassified into studies investigating internal source monitoring. In this way, action recognition tasks involving discrimination between actions that were either performed or imagined by the subject[19,22-25] and word recognition tasks involving discrimination between imagined and traced words[20] were reclassified as internal source-monitoring tasks (see Table 1)

Second, we observed a large heterogeneity across studies regarding the paradigm used to assess source-monitoring processes. These paradigms included either word, action, drawing voice or object recognition. However, despite this limitation, studies revealing significant differences between OCD-related symptoms and controls used either action or voice recognition tasks. This is in line with studies in patients with schizophrenia that highlighted reality-monitoring impairments using various paradigms, including action, word or speech recognition tasks[30], indicating that the identification of source-monitoring deficits is independent of the experimental paradigm.

Beyond the specificity of the task, the diversity in methods also highlights the importance of ecological validity when assessing source-monitoring performance. Such an approach seems particularly relevant not only in action recognition tasks where patients faced real life settings but also in item choices within tasks[31]. For instance, Constans *et al*[22], Cougle *et al*[23], Hermans *et al*[24] and Reese *et al*[26] investigated source monitoring for anxiety-evoking situations (turning on/turning off the lights). However, these studies did not report any significant impairment in patients, suggesting that this approach may not be useful for investigating source monitoring in patients with OCD. Furthermore, this large heterogeneity could partly

explain the inconsistencies observed between studies. The different categories of stimuli used in each of the retrieved studies (*e.g.*, neutral, OCD-relevant, personally relevant, bothersome, real-life action) limit any comparisons among studies, and therefore, any meta-analysis.

The present review also highlighted a large heterogeneity among studies regarding the included population. Indeed, the various studies investigated source monitoring in patients with general OCD symptomatology[24-29], in patients with OCD specifically displaying checking symptoms[19,20,22,23] and in subclinical checking-prone individuals[10,15,21]. Most studies failed to reveal any significant source-monitoring deficits. However, it should be noted that among 5 important studies[15,19,21,27,28], 4 revealed internal source-, reality-, or external source-monitoring deficits in checkers (clinical or subclinical) compared to noncheckers[15,19,21,27]. This suggests that a possible general deficit in discriminating the source of information may specifically affect subjects with checking compulsive behaviors. Current observations emphasize that research on source-monitoring deficits in OCD should consider the type of OCD as an essential variable (*i.e.*, checking, symmetry-ordering, contamination-washing, hoarding). Nevertheless, several studies we reviewed here show a great heterogeneity or even a lack of measurement of OCD symptoms, preventing us from distinguishing source-monitoring abilities across subgroups of patients[24-26,28,29,31]. Consequently, future research would benefit from considering the multidimensional property of OCD and incorporating a more comprehensive measure of OCD symptoms by a systematic use of standardized classifications such as the Yale-Brown Obsessive-Compulsive Scale[32,33].

Finally, several confounding factors were not controlled: the duration of the disease, age of onset were not reported, pharmacological treatments were either heterogeneous or not reported, and patients with comorbidities were excluded, included or not controlled. Moreover, although consistent differences between gender and ethnicity have been reported regarding OCD phenomenology[34,35], most of the studies retained in the current review did not provide results or did not assess their influence on source monitoring performances. Furthermore, the number of subjects included in the studies (from 12 to 48, mean across studies < 25) was too small to achieve sufficiently statistical power to conclude that there was no source-monitoring deficit associated with OCD's related symptoms, gender or ethnicity. Additionally, from a methodological point of view, some authors first investigated source monitoring in patients with OCD without a priori differentiating clinical subtypes but undertook an a posteriori comparison between checkers and noncheckers[24,25,27]. This approach did not allow an adequate a priori estimation of the sample size required to conclude with sufficiently statistical power. Another methodological limitation was the interpretation of negative findings based on p values using a frequentist approach. Further studies with Bayesian statistics could help us to determine whether to reject the null hypothesis.

A confidence impairment in general memory has been associated with OCD severity[36]. Here, the numerous studies reviewed reported a lack of confidence in source-monitoring functioning or a lack of global cognitive confidence. Interestingly, this lack of confidence has been found in both checkers[10,19,20,23] and noncheckers[20,24,25], suggesting that it is a cognitive marker for general OC symptoms. These findings raise the question of whether the participant's lack of confidence participates in his or her potential source-monitoring deficit. However, only three studies that revealed a significant source-monitoring deficit also investigated confidence, leading to heterogeneous results. Namely, a single study from Ecker *et al*[19] revealed positive results, whereas Zermatten *et al*[21] found no difference in confidence between groups, and Kim *et al*[28] found no correlation between source-monitoring results and confidence. This observation should be carefully considered since Kim *et al*[28] evaluated the participants' global cognitive confidence, whereas the other two studies specifically measured confidence in source-monitoring judgments. Future studies should systematically investigate the relationship between source-monitoring scores and source-monitoring confidence.

CONCLUSION

With most of studies concluding with negative results, the present review suggests a lack of global source-monitoring or specific internal source-monitoring deficits in patients with OCD. However, this review highlighted several methodological limitations regarding the tasks used and the statistical power of the included studies. A crucial factor to explain this is the age of the studies, which were published between 1983 and 2011. Future studies with sufficiently powered samples of patients

with OCD should consider the multidimensional property of OCD (*i.e.*, symmetry-ordering, contamination-washing, hoarding, aggressive obsession-checking, sexual-religious thinking), explore the subtypes of source-monitoring abilities (reality-, internal source-, external source-monitoring), and systematically investigate source-monitoring scores in relation with an evaluation of confidence in judgments.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Double-blind randomized controlled study of the efficacy, safety and tolerability of eszopiclone *vs* placebo for the treatment of patients with post-traumatic stress disorder and insomnia

Sheila M Dowd, Alyson K Zalta, Helen J Burgess, Elizabeth C Adkins, Zerbrina Valdespino-Hayden, Mark H Pollack

ORCID number: Sheila M Dowd (0000-0002-6032-0351); Alyson K Zalta (0000-0002-5159-8431); Helen J Burgess (0000-0003-3816-8194); Elizabeth C Adkins (0000-0002-0651-3013); Zerbrina Valdespino-Hayden (0000-0002-2188-5173); Mark H Pollack (0000-0002-3990-8337).

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Sheila M Dowd, Mark H Pollack, Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, IL 60601, United States

Alyson K Zalta, Department of Psychological Science, University of California Irvine, Irvine, CA 92697, United States

Helen J Burgess, Sleep and Circadian Research Laboratory, Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, United States

Elizabeth C Adkins, Center for Behavioral Intervention Technologies | Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, United States

Zerbrina Valdespino-Hayden, Department of Psychology, Montclair State University, Montclair, NJ 07043, United States

Corresponding author: Sheila M Dowd, PhD, Associate Professor, Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, 1645 West Jackson Blvd Suite 400, Chicago, IL 60601, United States. sheila_dowd@rush.edu

Abstract

BACKGROUND

Sleep disturbance is a core feature of post-traumatic stress disorder (PTSD). Given the relationship between sleep disturbance and PTSD, there has been a relative paucity of studies examining the potential therapeutic impact of using pharmacotherapy to target sleep disturbance in patients with PTSD. Eszopiclone (ESZ) is a non-benzodiazepine y-aminobutyric acid-A receptor agonist indicated for the treatment of sleep and may affect sleep in patients with PTSD.

AIM

To evaluate the efficacy of ESZ *vs* placebo (PBO) for patients with PTSD and insomnia.

METHODS

The study was a 12-wk, double blind, randomized controlled trial with 3 mg of ESZ (n = 13) or PBO (n = 12).

RESULTS

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Patients in both arms experienced significant improvement in PTSD symptoms as assessed by the Clinician-Administered PTSD Scale for DSM-IV (CAPS): ESZ (t11 = -3.12, *P* = 0.005) and PBO (t11 = -3.5, *P* = 0.002) and by self-report with the Short PTSD Rating Interview (ESZ t11 = -3.38, *P* = 0.003 and PBO t11 = -4.48, *P* = 0.0005). There were no significant differences between treatments on the CAPS (t22 = -0.13, *P* = 0.70) or the Short PTSD Rating Interview (t22 = -0.58, *P* = 0.56). Similarly, both treated groups improved on sleep measures as assessed by the Pittsburgh Sleep Quality Index with PTSD Addendum (PSQI) and on total sleep time (TST) and sleep latency assessed by actigraphy with no significant differences between groups (PSQI t22 = -0.24, *P* = 0.81; total sleep time t10 = 0.13, *P* = 0.90 and sleep latency t10 = 0.68, *P* = 0.50). There was a significant correlation between improvement in sleep and overall improvement in PTSD as measured by change scores on the PSQI and CAPS, r(8) = 0.79, *P* = 0.01 for ESZ treated subjects, but not for those treated with PBO r(9) = 0.16, *P* = 0.69. Adverse events of ESZ were consistent with the known profile of the medication including dysgeusia (30%, mild), sedation (20%, mild) and headache (20%, moderate to severe).

CONCLUSION
Results do not support the hypothesis of a specific positive effect of ESZ compared to PBO for measures of PTSD and associated sleep disturbance.

Key words: Trauma; Sleep disturbance; Hypnotic; Post-traumatic stress disorder

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Core tip: Sleep disturbance is a core feature of post-traumatic stress disorder (PTSD) yet few studies have examined the impact of psychopharmacotherapy. Results from this randomized controlled parallel study in individuals with PTSD and sleep disturbance did not demonstrate a significant relative improvement for eszopiclone (ESZ) *vs* placebo treated patients. Although patients receiving ESZ did experience significant improvement in measures of PTSD and sleep disturbance, placebo treated patients also significantly improved on these outcomes. Thus the potential role for ESZ in the treatment of PTSD remains uncertain until a larger more definitive trial is undertaken.

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INTRODUCTION

Sleep disturbance is a core feature of post-traumatic stress disorder (PTSD) and is reported by 70%-91% of patients with PTSD in civilian and combat veteran populations[1]. Dysregulated sleep is associated with a number of adverse consequences and in the aftermath of trauma exposure is a marker and perhaps risk factor for the development of PTSD or may contribute to its persistence[2-4]. Disturbed sleep among individuals with PTSD is associated with measures of poorer clinical status including depression and suicidality, poorer perceived physical health and somatization and increased rates of alcohol and substance use, and decreased overall quality of life and functioning[3,5-7]. In addition, sleep deprivation in preclinical studies led to impaired extinction learning in fear conditioned rats, a possible explanation for the impact of sleep disturbance a finding of potential relevance in explaining the persistence of PTSD in individuals with ongoing sleep disturbance[8].

Given the relationship between sleep disturbance and PTSD, there has been a relative paucity of studies examining the potential therapeutic impact of using pharmacotherapy to target sleep disturbance in patients with PTSD. Serotonin reuptake inhibitors including selective serotonin reuptake inhibitors and serotonin-

noradrenaline reuptake inhibitors are commonly used to treat PTSD. Sertraline and paroxetine are Food and Drug Administration approved for this indication however they were found to either worsen sleep disturbance or sleep was not assessed in individuals with PTSD[9]. The antidepressant trazodone, often used in low doses to treat insomnia, was reported effective for the treatment of PTSD as well as sleep disturbance in a small open trial[10]. Prazosin, an α_1-adrenergive receptor antagonist was found to be beneficial in reducing trauma related nightmares and overall global illness in several placebo (PBO) controlled trials in military and civilian PTSD patients[11]. A related compound, α-1 adrenergic antagonist doxazosin has been reported useful for PTSD related sleep disturbance in an open trial and also demonstrated efficacy in a randomized controlled trial of the extended release formulation for PTSD related sleep disturbance and overall PTSD symptoms[12,13]. Alternatively, studies of psychotherapy interventions found improvement in sleep quality and symptoms of PTSD. In a randomized controlled trial of sexual assault survivors using Imagery Rehearsal therapy a modified Cognitive Behavioral Therapy technique focused on sleep education, changing an aspect of a nightmare and rehearsing it daily, there was significant improvement in nightmares, sleep quality and overall PTSD symptoms[14,15].

Benzodiazepines are often used in the treatment of PTSD because of their anxiolytic and hypnotic effects. One clinical trial with alprazolam demonstrated no significant benefit for PTSD, and a small PBO controlled trial of clonazepam for PTSD-related sleep disturbance, reported no significant benefit for the benzodiazepine[16,17]. Treatment guidelines discourage the use of benzodiazepines in the treatment of PTSD because of lack of demonstrated efficacy, concerns related to abuse and dependence, and potential adverse impact on exposure based cognitive-behavioral therapy[18]. Among the non-benzodiazepine y-aminobutyric acid-A receptor agonist hypnotics several case reports of veterans treated with the hypnotic zolpidem showed improvement in PTSD associated insomnia[19].

Eszopiclone (ESZ) is a non-benzodiazepine y-aminobutyric acid-A receptor agonist indicated for the treatment of sleep onset and maintenance[20]. In addition to effects on primary insomnia, ESZ has been studied as augmentation to selective serotonin reuptake inhibitors for the treatment of major depression and generalized anxiety disorder[21,22]. In a small 7-wk crossover study, 3 wk of ESZ was associated with short-term improvement in overall PTSD severity as well as sleep disturbance[23]. In the present report, we present findings from a 12 wk randomized parallel PBO controlled trial to evaluate the relative efficacy, safety and tolerability of ESZ and PBO for the treatment of PTSD and associated sleep disturbance.

MATERIALS AND METHODS

The study was a 12-wk, double blind, randomized controlled trial with 3 mg of ESZ or PBO at bedtime with a one-month follow-up visit. Investigators were blind to the randomization sequence, which was designed by the Medical Center's research pharmacy. Recruitment began in September of 2012 and completed in 2015. Randomization was stratified by symptom severity as measured by a Clinician-Administered PTSD Scale for DSM-IV score of > 75 (CAPS)[24]. Safety evaluations, included assessment of medication use and drug allergies, and laboratory results (CBC, chemistry, pregnancy, thyroid function, EKG, urine toxicology screen and urinalysis). A study physician performed a medical history and physical exam and evaluated lab results to rule out excluded medical conditions. Diagnosis was determined with the Structured Clinical Interview for the DSM-IV[25].

The primary outcome measure to assess for efficacy for PTSD symptomatology was change in CAPS, which was assessed six times throughout the study. The CAPS is a 30-item, structured interview assessing the presence and severity of the DSM-IV PTSD criteria with demonstrated validity and reliability. The primary outcome measure for efficacy on sleep symptomatology was change in the Pittsburgh Sleep Quality Index with PTSD Addendum (PSQI), which was administered weekly[26]. The PSQI with PTSD Addendum is a 13-item, well-validated and reliable patient administered scale with higher scores reflecting poorer sleep.

The secondary outcome measures included the: (1) Short PTSD Rating Interview (SPRINT) to assess for PTSD symptomatology, a 10-item, valid and reliable clinician-administered scale assessing core and related symptoms of PTSD collected weekly; (2) Self-report sleep diary to assess for change in insomnia including sleep latency and total sleep time recorded daily for 12 wk; and (3) Actigraphy to assess for change in sleep, including total sleep time, initial insomnia and number of awakenings[27]. Actigraphy data was collected daily for the week between baseline and week 1 as well

as between week 11 and week 12. Additional clinician-rated instruments included a measure of depression and global clinical severity with the Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impression Scale[28,29]. A measure of global functioning was also completed using the Range of Impaired Functioning Tool (LIFE-RIFT)[30].

Inclusion and exclusion criteria

Subjects included male and female outpatients, aged 18-65 years of age with a primary DSM-IV diagnosis of PTSD and confirmed with CAPS score of > 45. Associated sleep disturbance was operationalized as (1) positive score on diagnostic criterion item D1: "difficulty falling or staying asleep"; (2) sleep latency > 30 min; and (3) total sleep time < 6.5 h at least three times per week over the previous month. A lifetime history of psychotic disorders was exclusionary, as was a history of alcohol/substance abuse in the last 3 mo. Concurrent use of antidepressants or benzodiazepines (on a stable dose for at least 6 wk) was allowed. Patients receiving current psychotherapy initiated within 3 mo of randomization or ongoing psychotherapy of any duration directed specifically toward treatment of PTSD and/or sleep disturbance (*e.g.*, CBT) were excluded, but general supportive individual, couple/family therapy > 3 mo duration was permitted. Patients who had current legal actions related to trauma or an ongoing relationship with their assailant were also excluded.

Informed consent

Informed consent was obtained prior to the initial assessment. The study was approved by the Institutional Review Board of Rush University Medical Center and was registered on ClinicalTrials.gov (Identifier: NCT01605253).

Statistics

The primary analysis used last observation carried forward approach in a modified intent to treat population that excluded subject who did not receive at least 1 dose of study drug. Baseline to endpoint (week 12) change scores were examined on the primary and secondary measures. All tests were 2-tailed with significance set at an α of 0.05. Correlations were completed comparing change scores on scales measuring sleep and PTSD.

RESULTS

There were no significant differences in demographics between groups at baseline. Of the 25 randomized subjects (13 ESZ, 12 PBO) 9 did not complete the study (ESZ = 6, PBO = 3). Four experienced worsening symptoms (2 ESZ, 2 PBO), 1 had memory disturbance (ESZ) and 4 were lost to follow up (3 ESZ, 1 PBO). Baseline demographics and clinical characteristics of the 25 randomized patients are presented in Table 1. The nature of the traumas included sexual assault or abuse (n = 6), physical abuse or assault (n = 6), observed violence to or death of a loved one (n = 3), military combat related trauma (n = 1), medical trauma (n = 2), car accident (n = 5), fire (n = 1) and accident (n = 1). A complete set of actigraphy data was obtained on a total of 12 subjects, 6 in the ESZ group and 6 in the PBO group. Only three subjects received concomitant medication, all in the PBO group, 2 received an antidepressant and 1 a benzodiazepine.

PTSD assessments

In the last observation carried forward, both treatment groups experienced significant improvement on the CAPS, (ESZ t11 = -3.12, P = 0.005 and PBO t11 = -3.5, P = 0.002) and the SPRINT (ESZ t11 = -3.38, P = 0.003 and PBO t11 = -4.48, P = 0.0005) (Table 2). However, there was no significant difference in outcome for ESZ *vs* PBO treated patients as reflected by the CAPS (t22 = -0.13, P = 0.70) nor the SPRINT (t22 = -0.58, P = 0.56). In a post-hoc analysis to determine if the core symptoms of PTSD were improved apart from effects on specific sleep symptoms, analyses were performed after removing the sleep items on the CAPS (item B2 and D1). There were no significant treatment effects for the remaining PTSD items of the CAPS (t22 = 0.25, P = 0.81).

Sleep assessments

There were no significant differences between ESZ and PBO on changes in the total score of the PSQI (t22 = -0.24, P = 0.81). Of the 12 subjects with complete actigraphy data, changes in total sleep time and latency were also not significantly different between ESZ and PBO (t10 = 0.13, P = 0.90 and t10 = 0.68, P = 0.50, respectively),

Table 1 Baseline demographic and clinical characteristics of patient (*n* = 25)

Characteristics	Eszopiclone (*n* = 13)	Placebo (*n* = 12)	Total sample (*n* = 25)
Age, mean ± SD	38 ± 11.6	48 ± 11.3	43 ± 12.2
Sex, male, *n* (%)	8 (54)	7 (58)	15 (60)
Race, *n* (%)			
White	4	2	6 (24)
African American	7	7	14 (56)
Hispanic	1	1	2 (8
Mixed	1	2	3 (12)
Education status, college graduate, *n* (%)	5	4	9 (36)
Duration of illness in years, mean ± SD	5 ± 7	7 ± 8	6 ± 8
Current comorbidity, *n* (%)			
Major depressive disorder	7	7	14
Social anxiety disorder	2	1	3
Generalized anxiety disorder	0	1	1
Lifetime depression, *n*	8	9	17
Lifetime alcohol or substance abuse or dependency, *n*	8	3	11
Concomitant antidepressant, *n*	0	2	2
Concomitant benzodiazepine, *n*	0	1	1
Drop-outs	6	3	9

consistent with results from the self-reported Total Sleep Time and Latency as assessed by the PSQI. In those treated with ESZ, there was a correlation between improvement in sleep and overall improvement in PTSD as measured by change scores on the PSQI and CAPS, r(8) = 0.79, P = 0.019. This was not true for those treated with PBO r(9) = 0.16, P = 0.69.

There was a correlation between the PSQI improvement and SPRINT improvement but this is the case only for the ESZ group r(8) = 0.89, P = 0.002 and not PBO at week 12 r(9) = 0.58, P = 0.10. In addition, there was a correlation in the ESZ group with improvement on TST with improvement on the SPRINT r(8) = -0.71, P = 0.05 but again, not in the PBO group r(9) = -0.51, P = 0.16.

Additional assessments

There were no significant differences in between ESZ and PBO change scores on the MADRAS (t22 = -0.73, P = 0.47) and the Clinical Global Impression - Severity Scale (t22 = 1.00, P = 1.00). Total change scores on the Range of Impaired Functioning Tool were also not significantly different between the two groups (t22 = 0.916, P = 0.369).

Adverse events

The most common adverse events experienced by subjects receiving ESZ were consistent with the known side effect profile for the drug and included dysgeusia (30%, mild), sedation (20%, mild) and headache (20%, moderate to severe). Adverse events in the subjects receiving PBO included most commonly dysgeusia (25%, mild) and a change in urine color or smell (25%, mild). Other adverse events in the PBO group included headache (16%, mild) and dry mouth (16%, mild). In order to enhance blinding, a trace amount of vitamin B was added to the PBO capsule, which may have contributed to some of these reported adverse events however was unlikely to affect sleep.

DISCUSSION

Results from this randomized controlled parallel study in individuals with PTSD and sleep disturbance did not demonstrate a significant relative improvement for ESZ *vs* PBO treated patients. Although patients receiving ESZ did experience significant improvement in measures of PTSD and sleep disturbance, PBO treated patients also significantly improved on these outcomes. Of note, improvement in PTSD symptoms as assessed by both clinician and self-reports for the ESZ but not PBO treated patients was correlated with improvements in sleep suggesting the potential importance of

Table 2 Outcome measures – completers

	Eszopiclone		Placebo			
Measure	**Baseline (mean ± SD)**	**Endpoint (mean ± SD)**	**Baseline (mean ± SD)**	**Endpoint (mean ± SD)**	***t* (*df*)**	***P* value**
CAPS total score	65 ± 22.04	40 ± 20.13	64 ± 10.93	41 ± 16.94	-0.13 (22)	0.70
SPRINT total score	22 ± 5.55	13 ± 6.58	24 ± 3.61	14 ± 4.79	-0.58 (22)	0.56
PSQI total score	12.58 ± 3.12	8.38 ± 3.35	12.33 ± 3.94	7.44 ± 2.31	0.24 (22)	0.81
Total sleep time	6.75 ± 2.11	7.00 ± 1.82	6.15 ± 1.74	6.78 ± 1.26	0.13 (10)	0.41
Sleep latency	31.11 ± 26.54	39.70 ± 48.16	44.06 ± 37.55	37.42 ± 26.27	0.68 (10)	0.77
MADRAS total score	24.25 ± 7.28	18.33 ± 9.59	25.56 ± 9.46	21.00 ± 10.80	0.73 (22)	0.47
CGI severity	4.42 ± 0.79	4.00 ± 0.95	4.50 ± 0.80	4.08 ± 0.79	0.00 (22)	1.00
LIFE-RIFT total score	13.50 ± 2.64	11.92 ± 4.14	13.58 ± 2.87	12.83 ± 3.22	0.92 (22)	0.37

CAPS: Clinician-Administered Post-Traumatic Stress Disorder Scale; SPRINT: Short Post-Traumatic Stress Disorder Rating Interview; PSQI: Pittsburgh Sleep Quality Index with Post-Traumatic Stress Disorder Addendum; CGI: Clinical Global Impression; LIFE-RIFT: Range of Impaired Functioning Tool.

this specific association for the active treatment *vs* PBO effect. Potential reasons for the negative findings in this study include the significant positive response of the PBO treated patients, the greater amounts of drop out amongst the ESZ *vs* PBO treated patients (50% *vs* 25%), and higher rates of past alcohol and substance abuse in the ESZ treated patients (62% *vs* 25%) with these latter two factors approaching but not achieving statistical significance given the small sample size.

This overall finding was in contrast to a report from an earlier small (n = 24) randomized PBO controlled crossover study with ESZ that demonstrated significant positive effects on PTSD and sleep for ESZ relative to PBO[22]. However, in that study, response to PBO was minimal, rate of drop out for both treatment groups was 7%, and the rates of past alcohol and substance abuse was lower (37%) than for ESZ treated patients in the current study.

Thus the potential role for ESZ in the treatment of PTSD remains uncertain until a larger more definitive trial is undertaken. In addition to the current negative study, a recent 26 wk multi-centered, double-blind PBO controlled study of prazosin in veterans from 13 Veterans Affairs Medical Centers found no benefit for the active agent over PBO or overall PTSD symptomatology[31].The data from insomnia focused CBT appears to improve sleep but no other symptoms of PTSD. However, the data from Imagery Rehearsal therapy for the treatment of PTSD is positive, suggesting a therapeutic role for affected patients[15]. Thus, further work is necessary to establish the potential role and patient population of sleep disturbance targeted pharmacotherapy for the treatment of patients with PTSD.

ARTICLE HIGHLIGHTS

Research background

Sleep disturbance is a frequent concern and an important component of post-traumatic stress disorder (PTSD). It is associated with several adverse consequences and may be a marker and risk factor for developing PTSD. It is also possible that it contributes to the difficulty treating PTSD. Preclinical studies have found impaired extinction learning in fear conditioned rats, a possible explanation for the impact of sleep disturbance.

Research motivation

There are few studies focused on the use of pharmacotherapy targeting sleep disturbance. However there is evidence that sleep disturbance among patients with PTSD are associated with increased rates of depression, suicidal ideation, increased use of alcohol and substances and poorer functioning.

Research objectives

The main objective was to examine the possible benefits of eszopiclone on sleep disturbance in PTSD.

Research methods

The study was a randomized controlled parallel study of participants with PTSD and sleep disturbance. We collected both self-report and clinician administered measures of PTSD and sleep quality. In addition, actigraphy data were collected and compared to patient's self-report sleep logs.

Research results

The study did not find a significant relative improvement for those treated with eszopiclone compared to placebo. Those participants receiving eszopiclone experienced significant improvement in symptoms of PTSD and sleep disturbance, as did the participants receiving placebo. However, clinician and self-report measures of PTSD were correlated with improvement in sleep for the eszopiclone, but not placebo-treated patients, suggesting the potential importance of this specific association for the active treatment *vs* placebo effect. Interestingly, there were greater amounts of dropouts amongst the eszopiclone *vs* placebo treated patients. In addition, there were higher rates of past alcohol and substance abuse in the eszopiclone treated patients with two factors approaching, but not achieving statistical significance. Due to the small sample size, the potential role for eszopiclone in the treatment of PTSD remains uncertain until a larger more definitive trial is undertaken

Research conclusions

The findings of this study have contributed to the mixed evidence exploring pharmacotherapy in the treatment of sleep disturbance in patients with PTSD.

Research perspectives

Further work is needed to determine the potential role for pharmacotherapy targeting sleep disturbance in patients with PTSD.

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EDITORIAL

Evidence for using dextromethorphan-quinidine for the treatment of agitation in dementia

Rajesh R Tampi, Pallavi Joshi, Padmapriya Marpuri, Deena J Tampi

ORCID number: Rajesh R Tampi (0000-0001-6754-6567); Pallavi Joshi (0000-0002-9622-4580); Padmapriya Marpuri (0000-0001-7407-4625); Deena J Tampi (0000-0002-4349-7622).

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Rajesh R Tampi, Department of Psychiatry and Behavioral Sciences, Cleveland Clinic Akron General, Akron, OH 44106, United States

Rajesh R Tampi, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH 44195, United States

Pallavi Joshi, Department of Psychiatry and Behavioral Sciences, Northwell Health-Staten Island University Hospital, Staten Island, NY 10306, United States

Padmapriya Marpuri, Department of Psychiatry, Einstein Medical Center, Philadelphia, PA 19141, United States

Deena J Tampi, Diamond Healthcare, Richmond, VA 23219, United States

Corresponding author: Rajesh R Tampi, MD, Chairman, Department of Psychiatry and Behavioral Sciences, Cleveland Clinic Akron General, Akron, OH 44106, United States. rajesh.tampi@yale.edu

Abstract

Behavioral and psychological symptoms including agitation are common in dementia, and are associated with decreased quality of life, increased risk of institutionalization, and greater patient and caregiver distress. Pharmacological agents used for management of behavioral and psychological symptoms of dementia are limited by their tolerability, prompting a need for identifying efficacious and safe pharmacological treatments for managing agitation in dementia. The combination of dextromethorphan and quinidine sulfate is approved for pseudobulbar affect, and may be effective in managing agitation in dementia. A review of literature found only one randomized controlled trial that evaluated the use of dextromethorphan-quinidine for the management of agitation in dementia when compared to placebo. Data from this trial demonstrated that dextromethorphan-quinidine decreased agitation in dementia, and was well tolerated. Although promising, further research is needed before dextromethorphan-quinidine combination can be accepted as a standard treatment for agitation in dementia.

Key words: Dextromethorphan; Quinidine; Agitation; Dementia; Behavioral and psychological symptoms of dementia

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Core tip: Dextromethorphan-quinidine is approved for the treatment of pseudobulbar affect and may be effective in managing agitation in dementia. There is only one published trial that has evaluated the use dextromethorphan-quinidine for agitation in dementia. The study was of good quality and found that dextromethorphan-quinidine decreases severity of agitation when compared to placebo. Additionally, dextromethorphan-quinidine was fairly well tolerated and did not appear to cause significant sedation or worsen cognitive symptoms among individuals with dementia.

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INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) are a group of psychological reactions, psychiatric symptoms and behaviors including agitation and aggression that are unsafe, disruptive, and impair the care of the individual in a given environment[1]. BPSD is seen in one-third of individuals with dementia who live in the community and in up to 80% of individuals with dementia who live in skilled nursing facilities[2]. The prevalence of agitation in dementia can be up to 46%, and is associated with decreased quality of life and increased risk of institutionalization for these individuals, in addition to greater caregiver burden and higher social and economic burden of caring for these individuals[3,4].

Non-pharmacological interventions are recommended as first-line for management of agitation in dementia. Pharmacotherapy including antipsychotics, antidepressants, anticonvulsants and cognitive enhancers are used when non-pharmacological interventions are ineffective[5]. Unfortunately, these medications are burdened with a significant side effect profile including QTc interval prolongation, weight gain, anticholinergic effects and cardiovascular adverse effects that carry substantial risks for the geriatric population[5]. Therefore, there is a great need for identifying efficacious and safe pharmacological treatments that are suitable for managing agitation in dementia.

Dextromethorphan is a low-affinity, uncompetitive N-methyl-D-aspartate receptor antagonist, σ1 receptor agonist, serotonin and norepinephrine reuptake inhibitor, and neuronal nicotinic α3β4 receptor antagonist[6]. Dextromethorphan has low and variable bioavailability when administered alone because of its rapid first-pass metabolism and subsequent elimination. The addition of quinidine, a potent inhibitor of the cytochrome P450 (CYP) liver enzyme CYP2D6, inhibits dextromethorphan metabolism and yields greater bioavailability[6]. The combination of dextromethorphan and quinidine sulfate is approved for the treatment of pseudobulbar affect in the United States and European Union. Evidence suggesting a potential effect of dextromethorphan-quinidine for agitation in dementia comes from controlled clinical trial data in non-demented patients with pseudobulbar affect[7].

The aim of this editorial is to review the literature on published randomized control trials (RCTs) that evaluated the efficacy and tolerability of dextromethorphan-quinidine for the management of agitation in dementia.

EVIDENCE FOR USIGN DEXTROMETHORPHAN-QUINIDINE FOR AGITATION IN DEMENTIA

A review of literature found only 1 RCT that evaluated the use of dextromethorphan-quinidine for the management of agitation in dementia (Table 1)[8]. The study was assessed as being of good quality based on JADAD criteria (Table 2). The details of the study are described in Table 3.

DISCUSSION

Available data from RCTs on the use of dextromethorphan-quinidine for the

Table 1 Summary of included studies

Ref.	Country of origin	Number of participants	Age (yr)	Setting	Comparators	Duration
Cummings *et al*[8], 2015	United States	220	50-90	Outpatient clinics, assisted living and nursing facilities	Dextromethorphan-quinidine *vs* placebo	10 wk

management of BPSD is extremely limited. The only trial that we found in our literature review evaluated the efficacy of dextromethorphan-quinidine in reducing severity of agitation among individuals with Alzheimer's disease when compared to placebo. This is the first dementia-related trial to use a sequential parallel comparison design[8]. In studies using this design, the first stage randomizes more patients to placebo than to active treatment. In the second stage, placebo non-responders from stage 1 are rerandomized and are included in the primary analysis. Pooled analysis of both stages maximizes the power to detect treatment differences and reduces the required sample size[8].

In this trial, treatment with dextromethorphan-quinidine demonstrated statistically significant decrease in agitation and aggression when compared to placebo. The reduction in agitation was considered clinically significant as measured by clinician rated scales. While the Alzheimer disease–related agitation characteristics of patients in this study were generally consistent with the International Psychogeriatric Association definition of agitation[8], patient emotional distress in patients was not directly measured.

Dextromethorphan-quinidine was generally well tolerated in this elderly population and was not associated with cognitive impairment. Most adverse events, including dizziness and diarrhea, were consistent with those observed in dextromethorphan-quinidine trials for pseudobulbar affect[8]. Falls were more common among patients receiving dextromethorphan-quinidine when compared to placebo. This may be explained by greater duration of exposure to dextromethorphan-quinidine and the lack of randomization to groups based on fall risk.

The strengths of the study include the use of the sequential parallel comparison design; inclusion of stable concomitant medications, including psychotropic medications, high retention rate, blinding of study sites to all aspects of the study, use of prespecified sensitivity analyses to corroborate the primary efficacy end point, and consistent results among multiple secondary outcomes and primary end point. Limitations of this trial include a short duration (10 wk), and a dose-escalation schedule that limited evaluation of dose-response relationships. Exclusion of concomitant drugs related to quinidine, tricyclic antidepressants, monoamine oxidase inhibitors, or phenothiazines, as well as cardiac parameters limit the generalizability of study findings. Finally, the patient population was predominantly outpatient, with only 5.5% of study participants domiciled in nursing homes. The treatment response may not be generalizable to patients in nursing homes and should be further explored.

In the study reviewed, the combination of dextromethorphan-quinidine was clinically efficacious for agitation and was generally well tolerated. However, evidence-based trials are limited, as is the generalizability of the results to wider clinical and nursing home populations. This highlights the need for further research on both the efficacy and safety of dextromethorphan-quinidine and other pharmacological interventions for agitation in dementia.

CONCLUSION

This review indicates that there is a scarcity of evidence for the use of dextromethorphan-quinidine for the management of agitation in dementia. There is only one available trial, which demonstrated a decrease in agitation and aggression compared with placebo. However, the trial had a limited number of participants and low representation of patients in nursing home, which further restricts the generalizability of the results. The need to further investigate the effectiveness of different pharmacotherapeutic modalities for the management of agitation in dementia is, therefore, essential.

Table 2 Quality of included studies

Ref.	Randomization	Similar groups initially?	Equal treatment?	Analyzed groups in which they were randomized	Objective/ "blind" treatments?	Overall quality of study
Cummings *et al*[8], 2015	Yes	Yes	Yes	Yes	Yes	Good

Table 3 Results summary from included studies

Ref.	Outcomes	Tolerability	Limitations
Cummings *et al*[8], 2015	In stage 1, mean NPI Agitation/Aggression scores were reduced from 7.1 to 3.8 with dextromethorphan-quinidine and from 7.0 to 5.3 with placebo, $P < 0.001$. In stage 2, mean NPI Agitation/Aggression scores were reduced from 5.8 to 3.8 with dextromethorphan-quinidine and from 6.7 to 5.8 with placebo, $P = 0.02$. The prespecified comparison of NPI Agitation/Aggression scores between patients who were randomized to receive only dextromethorphan-quinidine *vs* only placebo for the entire 10 weeks of the trial also favored dextromethorphan-quinidine over placebo, $P = 0.003$. Response to dextromethorphan-quinidine compared with placebo did not appear to differ by disease stage. The additional prespecified analysis that included both placebo responders and non-responders who were rerandomized in stage 2 did not alter the significance or magnitude of effect of the primary analysis. Sequential parallel comparison design analysis of prespecified secondary outcomes showed significant improvement favoring dextromethorphan-quinidine on global rating scores. Results for changes in the quality of life–Alzheimer disease score, ADCS activities of daily living Inventory, MMSE, and ADAS-Cog were not significant *vs* placebo. Post hoc analyses showed similar improvement in NPI Agitation/Aggression scores with dextromethorphan-quinidine in patients taking concomitant acetylcholinesterase inhibitors, memantine, antidepressants, or antipsychotics n when compared with those not receiving these agents. Lorazepam rescue medication was used by 6.6% of patients in the dextromethorphan-quinidine group during treatment and by 10.4% during treatment with placebo	Treatment-emergent adverse events were reported by 61.2% of patients in the dextromethorphan -quinidine group and 43.3% with placebo group. The most commonly occurring treatment-emergent adverse events were falls (8.6% *vs* 3.9%), diarrhea (5.9% *vs* 3.1%), urinary tract infection (5.3% *vs* 3.9%), and dizziness (4.6% *vs* 2.4%). Serious adverse events occurred in 7.9% patients receiving dextromethorphan-quinidine and in 4.7% of patients receiving placebo. Serious adverse events in patients receiving dextromethorphan-quinidine included chest pain ($n = 2$), anemia, acute myocardial infarction, bradycardia, kidney infection, femur fracture, dehydration, colon cancer, cerebrovascular accident, aggression, and hematuria. Serious adverse events in patients receiving placebo included idiopathic thrombocytopenic purpura, vertigo, pneumonia, gastroenteritis, contusion, transient ischemic attack, and agitation. Eight patients (5.3%) receiving dextromethorphan-quinidine and 4 (3.1%) receiving placebo discontinued treatment owing to adverse events. No deaths occurred during the study. No clinically meaningful between-group differences in electrocardiographic findings were observed	The duration was limited to 10 wk. The dose-escalation schedule limited evaluation of dose-response relationships. Exclusion of concomitant drugs related to quinidine and specific electrocardiographic/cardiac parameters that restricted patient enrollment, may limit the generalizability of study findings. Treatment at experienced trial sites by specialized clinicians under a clinical protocol prescribing frequent assessments may not reflect general practice. The patient sample consisted predominantly of outpatients; agitation in nursing home residents was underrepresented

NPI: Neuropsychiatric inventory; ADCS: Alzheimer's disease cooperative study; MMSE: Mini mental state examination; ADAS-Cog: Alzheimer disease assessment scale–cognitive subscale.

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REVIEW

Moderators and mediators of antipsychotic response in delusional disorder: Further steps are needed

Alexandre González-Rodríguez, Armand Guàrdia, Diego José Palao, Javier Labad, Mary V Seeman

ORCID number: Alexandre González-Rodríguez (0000-0003-1855-8566); Armand Guàrdia (0000-0002-3908-0875); Diego José Palao (0000-0002-3323-6568); Javier Labad (0000-0003-2214-1886); Mary V Seeman (0000-0001-6797-3382).

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Alexandre González-Rodríguez, Armand Guàrdia, Diego José Palao, Javier Labad, Department of Mental Health, Parc Taulí University Hospital, Autonomous University of Barcelona, Sabadell 08280, Spain

Mary V Seeman, Department of Psychiatry, University of Toronto, Toronto, ON M5P 3L6, Canada

Corresponding author: Mary V Seeman, DSc, FRCP (C), MD, Emeritus Professor, Department of Psychiatry, University of Toronto, 260 Heath Street West, Suite #605, Toronto, ON M5P 3L6, Canada. mary.seeman@utoronto.ca

Abstract

Delusional disorder (DD) has been traditionally considered a relatively rare and treatment-resistant psychotic disorder. In the last decade, increasing attention has focused on therapeutic outcomes of individuals affected by this disorder. The aim of this paper is to provide a synthesis of the literature addressing two very important questions arising from DD research: (1) For which patients with DD do antipsychotic medications work best (the moderators of response); and (2) What variables best explain the relationship between such treatments and their effectiveness (the mediators of response). We searched PubMed and Google Scholar databases for English, German, French and Spanish language papers published since 2000. We also included a few classic earlier papers addressing this topic. Variables potentially moderating antipsychotic response in DD are gender, reproductive status, age, duration of illness, the presence of comorbidity (especially psychiatric comorbidity) and its treatment, brain structure, and genetics of neurochemical receptors and drug metabolizing enzymes. Antipsychotic and hormonal blood levels during treatment, as well as functional brain changes, are potential mediating variables. Some, but not all, patients with DD benefit from antipsychotic treatment. Understanding the circumstances under which treatment works best can serve to guide optimal management.

Key words: Delusional disorder; Psychosis; Moderators; Mediators; Antipsychotic response

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Core tip: Although patients with delusional disorder have traditionally been viewed as treatment-resistant, many do experience benefits from antipsychotic medications, but not all respond similarly. The identification of mediators and moderators of treatment

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response is clinically useful in that understanding under what circumstances treatment works best provides a reliable guide to effective management.

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INTRODUCTION

Delusional disorder (DD) is defined in DSM-5 as a psychotic disorder characterized by the persistence, for at least one month, of one or more delusions that do not markedly impair personal, social or occupational function and that are present independently of schizophrenia, affective disorder or substance abuse disorder[1]. The disorder is characterized by a high prevalence of psychiatric morbidity. Delusional beliefs in this condition are encapsulated and usually monothematic; they lack the bizarreness of delusions found in schizophrenia[2]. The various commonly seen delusional themes designate subtypes of DD - *e.g.*, erotomania, grandiosity, delusional jealousy, paranoia, and somatization[3]. DD has been widely considered a relatively rare disorder with a cited lifetime prevalence of 0.02%[1,4]. It is a disorder that starts relatively late in life; the mean onset age is 40, but this ranges from 18 to the nineties. The disorder is somewhat more common in women than in men[5,6]. The individual's ethnic and religious background is an important consideration when making a diagnosis; it determines whether a strongly held irrational belief is a delusion or a traditional mindset.

DD has been described by Kendler[7] as an inherently treatment-resistant disorder but others have challenged this view, attributing most of the failure to respond to treatment to widespread non-adherence. Individuals with this disorder characteristically do not see themselves as ill, and, therefore, often do not take prescribed drugs[8-10].

As in other diseases, there has been a growing interest in the field of DD studies to enable the monitoring of both adherence and response to therapeutic drugs[11]. However, to the best of our knowledge, to date, no clinical trials have been conducted on the effectiveness of currently used medications, which renders specific treatment recommendations impossible to make at this time[10]. Only one randomized controlled trial of treatment effectiveness exists in DD and this has evaluated a psychotherapeutic approach rather than a pharmacological one. The trial evaluated group cognitive-behavioral therapy *vs* supportive group therapy conducted over a 24-wk period[12]. Cognitive-behavioral therapy proved to be more effective than the control measure on 3 of 7 dimensions of the Maudsley Assessment of Delusion Schedule, but the participant sample was very small (12 participants per group).

One problem in investigating treatment outcomes in DD is the lack of consensus on the definition of antipsychotic response as it applies to this disorder[13]. Different investigators use different definitions of response and many base their judgement solely on a clinical evaluation, which is, by its nature, necessarily subjective. Cut-off points on assessment scales are sometimes used, but the scales differ[14]. Adding to the problem is the difficulty of accurately assessing issues of adherence[11,15].

Despite difficulties in evaluating treatment outcomes, most reports agree that response is variable and heavily dependent on patient factors, such as adherence to the prescribed regimen[16].

Patient pre-existing characteristics that influence response are referred to as moderators. Several have been suggested in the context of DD. Identifying a moderator helps to determine when and under what conditions treatment is most effective, and for whom[17-19]. In contrast, a mediator, or intervening variable, is one that can alter the relationship between the independent and dependent variables, in this case, antipsychotic treatment and outcome[18,19]. Moderators are in place before treatment begins. Mediators mediate the process during treatment. Moderators of treatment efficacy are inherent in the patient or the patient's environment. Mediators of treatment efficacy are measurable changes in the patient that occur during the course of treatment[20] (Figure 1).

Moderators and mediators of an intervention are important to identify. They have

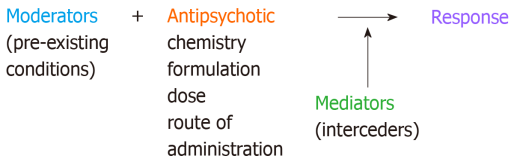


Figure 1 Moderators and mediators.

never been reported for DD but have been specifically addressed in other psychiatric domains, for instance, in affective disorders and substance abuse[21-23].

Specifying moderator and mediator factors in DD clarifies such questions as: For whom do available treatments work, how do they work, and when do they work.

LITERATURE SEARCH

We searched PubMed and Google Scholar databases for English, German, French and Spanish language papers published since 2000 that pertained to the role of moderators and mediators of antipsychotic response in DD. Several thousand abstracts were initially screened. Most were excluded because, although they addressed predictors, mediators, and moderators of antipsychotic response, they did so for schizophrenia only. In the end, by consensus, 40 primary articles were selected as relevant to our goals. These included a few classic earlier papers on the topic that we considered to be still relevant. For purposes of comparison, additional papers addressing moderators/mediators in psychoses other than DD were also included. After the screening and selection process, the collected information was divided into the following sections: (1) Moderators of treatment response in DD; and (2) Mediators of treatment response in DD.

MODERATORS OF TREATMENT RESPONSE

In other psychotic disorders, moderating variables, or pre-treatment characteristics of patients that predict response to drugs, have included gender, reproductive status, age at treatment, duration of illness, psychiatric comorbidity, abnormalities of brain structure or function, aberrant biochemistry, and gene variants, especially those coding for neurochemical receptors and drug metabolizing enzymes (Table 1). In DD, consideration of moderating variables involved in antipsychotic response has not been previously attempted.

Gender and hormonal status

There is a literature on gender differences in DD. As part of the Halle Delusional Syndromes Study, Wustmann *et al*[24] investigated gender-related features of DD in a carefully diagnosed sample of 43 inpatients (22 men and 21 women) consecutively admitted to one hospital over a long period of years. Thirty-three patients were re-interviewed from 3 to 24 years after the onset of their symptoms. Gender distribution in this sample was almost equal; age of onset was significantly later in women; the diagnosis persisted in women whereas, in a third of the men, it was changed to schizophrenia over time. Women were more compliant with treatment and, thus, received medication more often than men. Paradoxically, while over 80% of the women remained unremitted at follow up, this was true for only half of the men. The authors concluded that DD in women is more severe and more persistent than in men, but this study does not directly address the effect of gender on treatment response[24].

Román Avezuela *et al*[25] investigated gender differences in DD in a sample of 50 first admission inpatients. All were diagnosed according to DSM-IV criteria and were retrospectively evaluated by review of medical records, the OPCRIT 4.0, and a symptom inventory specially designed for the study. The proportion of women to men was 1.27:1. As in the Wustmann *et al*[24] study, the age of first admission was higher in women. Men misused substances more than women and women suffered depression more often than men. Men were more likely to present with grandiose, jealous or persecutory delusions whereas women more frequently had erotomaniac delusions. No gender differences in the course of illness were observed but, again, treatment response was not directly examined[25].

These two studies yielded some similar and some contradictory results, which is to be expected because sample sizes were small and methodologies differed. Even with

Table 1 Potential moderators and mediators of antipsychotic response in delusional disorder

Moderators	Mediators
Gender	Antipsychotic plasma concentrations
Reproductive status	Blood flow to brain
Age	Brain glucose metabolism
Comorbidity	Dopamine receptor occupancy
Brain lesions	Estrogen levels
Genetic factors	
D2 receptor genes	
Metabolizing enzyme genes	

identical methodology, results of gender studies can easily diverge because a variety of potential moderating variables differ by gender, comorbid substance use and treatment adherence for instance, and this can skew group gender response in opposing directions depending on the composition of the sample[5].

In patients with psychoses other than DD, women have been observed to respond more robustly to antipsychotics than men, but only during their reproductive years[26,27]. This has been attributed to estrogens potentiating treatment response[28-30], a potentiation that has been shown to end at menopause[31]. DD begins relatively later in life than schizophrenia so that most women with this disorder cannot count on circulating estrogens to assist with antipsychotic response. In fact, the drop of estrogen at menopause may be what determines the higher prevalence of DD in women than in men[6].

When studies that control for potentially confounding factors are conducted in DD, it seems likely that gender will prove to be a moderator of antipsychotic response, as it is in other psychoses.

Age

Age is known to moderate antipsychotic response in many psychotic illnesses. Both age at treatment and also age at onset of illness, often a proxy for illness duration, can impact therapeutic outcomes in psychosis.

Mangoni *et al*[32] have highlighted a person's age at treatment as a moderator of medication response. Age changes the bioavailability, distribution, metabolism and elimination of drugs. As people age, there is a gradual reduction in renal and hepatic clearance, as well as a relative increase in the volume of drug distribution[33]. The net effect for lipophilic drugs such as antipsychotics is a tendency for drug accumulation in lipid stores[34], which can lead to drug toxicity. Toxic drug levels impair subsequent adherence, thereby undermining treatment effectiveness. To date, no studies have specifically investigated the impact of age at treatment on therapeutic outcomes in DD. Conclusions can only be inferred from studies in schizophrenia populations and from other pharmacological research in aging populations.

Age at onset of illness has been considered a moderator of antipsychotic response in schizophrenia[35]. Usually, the younger the onset, the more severe the illness, which equates with poor response to treatment[35]. With respect to DD, the severity of symptoms has not generally been seen as varying with onset age although the results of the Wustmann *et al*[24]'s study do suggest that later onset correlates with symptom severity. DD almost always starts relatively late in adult life when the physiological and psychological process of aging and age-related co-morbidities make recovery from any illness increasingly challenging. This undoubtedly contributes to the generally poor antipsychotic response in DD. It is possible that larger samples will, nevertheless, find that, here too, younger onset correlates with illness severity. Young onset age usually means longer duration of illness at the time of ascertainment. In most illnesses, long untreated duration makes recovery less likely[36], but the relevant studies in DD have not been done. Interestingly, DD subtypes seem to differ with respect to age at onset. Out of 51 outpatients diagnosed with DD at one psychiatric clinic, the persecutory subtype showed the oldest onset age while the youngest onset age was associated with the somatic subtype[37].

In general, age, whether at the time of treatment or at the time of onset of symptoms, is a powerful moderator of treatment outcome in psychosis[38] and may prove to be so in DD as well.

Comorbid psychiatric disorders

It is known that patients with DD suffer from many psychiatric comorbidities,

especially depressive disorders[39]. Mood disorders are reportedly seen in one half of patients with DD[40].

Maina *et al*[39] investigated the occurrence and clinical correlations of comorbid psychiatric diagnoses in 64 patients with DD. Patients with one comorbid psychiatric disorder (as compared to those with no co-morbidity) showed an earlier age of DD symptom onset, came to psychiatric attention at an earlier age, and were, as a group, younger. Antipsychotic response was, however, not evaluated[39]. Other research groups have confirmed the extent of comorbidity in DD. In a study of 86 outpatients with DSM-IV DD, and using the Mini International Neuropsychiatry Interview as a diagnostic tool, de Portugal *et al*[40] found that 46.5% of study participants suffered from at least one additional lifetime psychiatric diagnosis, depressive disorder being the most common one. This is in agreement with Marino *et al*[41] who reported that, in 42% of 67 patients with DD (44 women and 23 men), a mood disorder had preceded the onset of DD.

Substance abuse may also precede DD. Román Avezuela *et al*[25], in the study referred to earlier, showed that men frequently suffered from alcohol or cannabis dependence at least one month prior to the diagnosis of DD. Depression and substance abuse comorbidity are both associated with a worse prognosis in DD[25,41], especially if the comorbid condition precedes the onset of DD symptoms.

In psychotic illness in general, substance abuse is a frequently seen secondary condition[42,43], a way, some have speculated, of coping with disturbing thoughts or with medication side effects. In one study from India, 11 out of 13 first episode, drug-naive DD patients from a tertiary care center were found to suffer from at least one psychoactive substance use disorder[43]. Since these patients were unmedicated, the substances were probably used to drown out disturbing thoughts, although it is also possible that the effect of early onset substance use may have contributed to the induction of DD.

The connection between comorbid psychiatric diagnoses and antipsychotic treatment response has not been sufficiently investigated in DD. When it is, it may prove to significantly moderate antipsychotic response, as it does in related illnesses.

Brain changes on neuroimaging

Structural and functional brain changes have been reported in neuroimaging case studies of patients with DD[44], giving rise to the possibility that such changes may moderate treatment response.

In 1989, Miller and co-workers carried out a prospective study on a sample of patients with late-life onset psychosis. Five patients (3 diagnosed with DD, 1 with schizophrenia, and 1 with bipolar disorder) underwent either magnetic resonance imaging or computed tomography. The investigators found that multiple lacunar infarcts were associated with poor neuropsychological performance and non-response to treatment. They suggested that the presence of brain structural lesions could predict treatment response[45]. A similar correlation between brain lesion and treatment failure has been seen in schizophrenia[46,47]. Freudenmann *et al*[48] have reported fronto-striato-thalamo-parietal network lesions that correlated with antipsychotic response in one patient with delusional parasitosis.

Other neuroimaging studies in DD, however, have been unable to show a correlation between brain structure and therapeutic response[49,50]. Howard and collaborators, for instance, found that lateral ventricle volumes in DD were greater than in schizophrenia, but they could not show an association between this finding and response to antipsychotic medications[50].

As of now, it is unclear what brain lesion, if any, predicts antipsychotic response in DD patients.

Biological factors: Biochemistry and genetics of receptors and enzymes

Hyperdopaminergic states have been implicated in many psychoses[51], buttressed by the fact that all antipsychotic drugs currently in use block D2 dopamine receptors, as elucidated by the pioneering work of Philip Seeman[52] and reconfirmed many times over the years[53,54]. Since one-third of patients with schizophrenia show poor response to available antipsychotics, the implication is that the dysregulation of other neurochemical pathways (serotonergic, cholinergic, glutaminergic) may also, to varying degrees, lead to psychosis[55-58].

Morimoto *et al*[59] investigated the relationship between antipsychotic response, plasma homovanillic acid (pHVA), dopamine receptor (DR) genes and tyrosine hydroxylase (TH) in 57 patients with DD, 48 patients with schizophrenia, and 48 healthy controls. DD patients homozygous for the Ser9Ser dopamine D3 receptor (DRD3) genetic variant showed higher pretreatment levels of pHVA, -*i.e.* higher dopamine function, than heterozygous (Ser9Gly) patients. The pHVA level fell (by nearly 30 pmol/mL) after 8 weeks of treatment with the antipsychotic, haloperidol,

suggesting that polymorphisms in the DRD3 gene can moderate response to antipsychotics.

It has been reported that genetic variants of cytochrome P450 enzymes responsible for antipsychotic drug metabolism either raise or lower antipsychotic plasma levels of specific drugs, and can thus contribute to treatment response[60]. Recent work has investigated the benefits of pharmacogenetics in maximizing antipsychotic treatment effectiveness in psychosis. The study sample included 58 patients with DD. When dose adjustments were made to antipsychotic drugs according to the presence of relevant polymorphisms in CYP1A2, CYP2C19, CYP2D6 and CYP3A5 enzymes, an improved symptom response was expected. Unfortunately, this was not found[60]. Genetic variants of CYP2D6 enzymes have been able, however, to predict which doses of which drugs result in side effects[61].

Subtherapeutic plasma levels of antipsychotics, attributable to activity differences in CYP enzymes (among other factors that occur during the course of treatment), are held to be a major cause of treatment resistance in most psychoses[62]. The investigation of genetic variants of genes encoding for cytochrome P450 enzymes has revealed that some patients are fast or ultra-fast metabolizers, while others metabolize drugs much more slowly. Speed of metabolism affects serum concentration and subsequent entry into the brain.

Therapeutic drug monitoring is a promising new area in DD. As early as 1998, Silva and co-workers explored the effect of giving pimozide at increasing doses to 7 patients with DD over a 6-wk period. Pimozide levels and psychopathology scores as per the Brief Psychiatric Rating Scale (BPRS) were assessed every week[63]. Had some patients improved, this study could have yielded a plasma concentration/therapeutic response index. Unfortunately, pimozide had no effect on any dimension of the BPRS, although pimozide levels confirmed that patients were taking their medication.

Therapeutic effectiveness can, as mentioned earlier, be defined in a variety of ways. Herbel and Stelmach conducted a study where they defined effectiveness as the restoration of decisional competence in previously incompetent patients with DD[64]. This outcome was determined in their study by retrospective chart review. Where the plasma level of haloperidol was done (only one case), a low level (2.9 ng/mL) was associated with failure to achieve competence.

More recently, antipsychotic plasma concentrations obtained by high-performance liquid chromatography in 27 patients with DD and 27 patients with schizophrenia were used to examine treatment both adherence and response[65]. The association between antipsychotic response and plasma levels of antipsychotics could not be determined, however, due to the naturalistic design, the several antipsychotics with which patients were treated, and the relatively small sample size[65].

The serum concentration of a drug is affected, of course, by more than genetic variants of metabolizing enzymes. Given strict adherence to a prescribed regimen, it is primarily determined by drug dose, but also by route of administration, by liver and kidney health, volume of distribution, and by interaction with concomitant drugs, tobacco, and the ingestion of specific foods[66]. Some of these factors are moderators of response; some are mediators.

Available evidence from patients with other psychoses[62,67,68] suggests that the determination of plasma drug concentrations, especially when the antipsychotic in question is clozapine, is very useful in predicting treatment outcome. If, in the future, antipsychotic plasma concentration are linked to response in DD, then genetic variants of cytochrome P450 enzymes that help to determine antipsychotic blood levels will be categorized as moderators of response, as they are in other psychoses.

MEDIATORS OF TREATMENT RESPONSE IN DD

Several mediators of response (factors that emerge from the interaction of patient and antipsychotic treatment) have been identified in patients with DD: Antipsychotic drug levels, functional changes in the brain, and hormonal levels (see Table 1).

Plasma level of the drug

As mentioned, and as is well known, the blood level of an antipsychotic drug predicts how much of it will enter the brain and, thus, how effective it will be at its target site. Blood level is determined by many factors, some of which are moderators (genetics of metabolizing enzymes, genetics of drug receptors, genetics of body mass, genetics of liver and kidney health) because they characterize the person prior to treatment, and some of which are mediators because they occur during treatment (drug dose, route of administration, smoking status, concomitant drugs, ingestion of certain foods such as grapefruit, which can raise the blood level of some drugs and lower the level of

others).

As described earlier, plasma levels of antipsychotics have been examined in DD but it has not yet been possible to correlate them with treatment response.

Functional brain changes during treatment

In schizophrenia, many investigations have been conducted into the relationship between changes in regional blood glucose metabolism (measured by single-photon emission tomography - SPECT) and clinical response to antipsychotic treatment. Cerebral blood flow (CBF) to different regions of the brain has also been studied in a variety of patients undergoing treatments with antidepressants, antipsychotics, and electroconvulsive therapy[69-73].

In DD, specifically in delusional parasitosis, cerebral blood flow changes before and after successful treatment with antipsychotics have also been reported. Narumoto and colleagues described the case of an 82 year old man who had had symptoms of delusional parasitosis for 5 years beginning one month after he suffered a stroke in the right temperoparietal region of the brain[74]. Cerebral blood flow in the patient was assessed at baseline by SPECT and again after 6 weeks of risperidone therapy, by which time the patient had fully recovered from his delusional symptoms. At baseline, there was a global decrease of CBF, which the investigators attributed to the influence of the prior stroke. Post-treatment SPECT, however, showed a marked increase in regional cerebral blood flow (rCBF) in bilateral frontal and left temperoparietal regions. The decreased rCBF in the right temperoparietal region remained unchanged. Increased blood flow to large brain regions other than the lesion area seems to have mediated the improvement of clinical symptoms[74].

Freudenmann *et al*[48] described another case of a 27 year old woman with delusional parasitosis who was treated with aripiprazole. She achieved full remission when dopamine 2 receptor occupancy reached 63%-78% occupancy, as measured by photon emission tomography[48]. Using SPECT, cerebral glucose metabolism was also investigated in this patient. Before treatment, glucose metabolism in the thalamus and putamen was left dominant. This remained unchanged after treatment.

Although only individual case reports exist at this time, functional neuroimaging changes may prove, in the future, to be quantifiable mediators of antipsychotic response in DD (Table 2).

Changes in hormonal levels

In other psychoses, various hormonal levels have been investigated as potential mediators of treatment response. Many preclinical, clinical and epidemiological studies have concluded that elevated estrogen levels are neuroprotective in psychosis[75-78], which would partly explain why schizophrenia in women, until the age of menopause, is, on the whole, a less severe disease than it is in men[26,79]. Hypothetically, normal fluctuations of estrogen levels influence the response of psychotic symptoms to antipsychotic treatment either by action at the dopamine 2 receptor or by modification of the activity of drug metabolizing agents.

During the reproductive years, the level of estrogen in women fluctuates with menstrual phase and also with pregnancy stage[78,79]. This is reflected in clinical measures of the severity of symptoms; the higher the level of estrogen, the more attenuated the symptoms[80].

Because DD is a disorder of older age, fluctuating estrogen levels may not be as relevant as they are in schizophrenia[81,82] but, by checking hormone levels, one would be able to determine whether exogenous estrogens (and perhaps other hormones) can boost antipsychotic response in DD.

CONCLUSION

Although many patients with DD experience benefits from treatment with antipsychotics, this is not true for all patients. Understanding for whom and under what circumstances treatment works best can guide management strategies for DD patients. Based on the literature on DD and other psychoses, moderators of antipsychotic response probably include gender, reproductive status, age, comorbid psychiatric disorders, baseline brain abnormalities, biochemistry, and genes coding, for instance, for brain receptors and drug metabolizing enzymes. Suggested mediating variables include measurable functional brain alterations during treatment, such as changes in neuronal receptor occupancies, blood flow to the brain, brain glucose metabolism, and blood hormone levels.

Understanding moderators has substantial clinical relevance. For instance, knowing that comorbid psychiatric illness such as mood disorders and substance abuse disorders often precede DD opens an avenue to early intervention. Understanding

Table 2 Therapeutic implications of brain lesions in delusional disorder

Ref.	Study design	Imaging method	Age	Contrast group	DD type	Main findings
Moderators of treatment response (structural brain findings)						
Miller *et al*[45], 1989	Prospect	CT, MRI	Case 1: 86 Case 2: 72 Case 3: 62	Schizophr (n = 1) Bipolar disorder (n = 1)	Persecutory	Structural brain disease in all 3 cases contributed to treatment resistance
Mediators of treatment response (changes in functional brain findings)						
Wada *et al*[69], 1999	Case report	SPECT	Age = 78	-	Somatic	Reduced regional cerebral blood flow in the left temporal and parietal lobes improved at remission
Ota *et al*[70], 2003	Case report	SPECT	Age = 72	-	Somatic	Decreased perfusion in the left temporal and parietal lobes improved after treatment
Hayashi *et al*[71], 2004	Case report	SPECT	Age = 77	-	Somatic	Reduced regional cerebral blood flow in the left temporal and parietal lobes improved after treatment
Narumoto *et al*[74], 2006	Case report	SPECT	Age = 82	-	Somatic	Global decrease in rCBF Reversed in all non-stroke areas after remission
Hayashi *et al*[72], 2010	Case report	SPECT	Age = 42	-	Somatic	Reduced regional cerebral blood flow in the left temporal and parietal lobes normalized after treatment
Freudenmann *et al*[48], 2010	Prospect.	PET SPECT	Age = 27	Organic DD (n = 1)	Somatic	*SPECT*: D2R occupancy predicted remission *PET*: Glucose metabolism in putamen and thalamus did not normalize with remission
Uezato *et al*[73], 2012	Case report	SPECT	Age = 53	-	Somatic	Hyperperfusion in the right temporal lobe normalized after electroconvulsive therapy

DD: Delusional disorder; CT: Computerized tomography; MRI: Magnetic resonance imaging; SPECT: Single photon emission computed tomography; rCBF: Regional cerebral blood flow; PET: Positron emission tomography. DaT: Striatal dopamine transporter; D2R: D2 receptor.

mediating factors in DD patients who are adherent to medication but nevertheless not responding helps clinicians by suggesting different ways (other than raising the dose) by which plasma levels can be increased, for instance via smoking cessation, changes in diet or drug regimes, or by the addition of adjunctive hormones.

DDs have been traditionally difficult to treat. Awareness of the moderators and mediators of treatment response can help to make recovery possible.

FUTURE DIRECTIONS

The identification of moderators and mediators of response in delusional disorders, which traditionally do not respond well to standard antipsychotic treatment, facilitates the development of personalized treatments. A better understanding of

these factors will help clinicians decide which form of treatment works best for which patient[60].

Several moderators of antipsychotic response in delusional disorder have been suggested: Gender, reproductive status, age and comorbid medical disorders, comorbid psychiatric disorders, baseline brain abnormalities, biochemical factors, genetics of both liver enzymes and neurochemical receptors in the brain[39,44,59]. In the future, randomized controlled trials will need to ascertain whether these or other factors do, indeed, moderate response in DD.

Future studies will also need to investigate potential mediating variables of antipsychotic response in DD, such as functional brain changes, antipsychotic plasma levels and estrogen and other hormone levels.

Delusional disorder may respond better to psychotherapeutic interventions than to medications. Moderators and mediators of cognitive behavioral therapies, for instance, will need to be investigated in the future.

All subcategories of DD may not respond in the same way to treatment. Currently, most studies have only researched the somatic subtype[48,49]. It is possible that patients with erotomania or delusional jealousy respond differently than those with delusional parasitosis – this question needs to be thoroughly examined.

The future will undoubtedly be able to overcome the problem of research sample availability of relatively rare conditions such as delusional disorders. Large international collaborations will almost certainly be part of the solution.

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ORIGINAL ARTICLE

Basic Study

Comparison of novel tools with traditional cognitive tests in detecting delirium in elderly medical patients

David J Meagher, Henry O'Connell, Maeve Leonard, Olugbenga Williams, Fahad Awan, Chris Exton, Michael Tenorio, Margaret O'Connor, Colum P Dunne, Walter Cullen, John McFarland, Dimitrios Adamis

ORCID number: David J Meagher (0000-0001-8324-8017).

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David J Meagher, Henry O'Connell, Maeve Leonard, Olugbenga Williams, Fahad Awan, Margaret O'Connor, Colum P Dunne, Walter Cullen, John McFarland, Dimitrios Adamis, Cognitive Impairment Research Group, Graduate Entry Medical School, University of Limerick, Limerick V94 YVHO, Ireland

Chris Exton, Michael Tenorio, Department of Computer Sciences, University of Limerick, Limerick V94 YVHO, Ireland

Walter Cullen, School of Medicine, University College Dublin, Dublin 4 D04 V1W8, Ireland

Dimitrios Adamis, Sligo Mental Health Services, Ballytivan, Sligo F91 CD34, Ireland

Corresponding author: David J Meagher, MD, PhD, Chairman, Professor, Head, Department of Psychiatry, Graduate Entry Medical School, University of Limerick, Limerick V94 YVHO, Ireland. david.meagher@ul.ie

Abstract

BACKGROUND

Efficient detection of delirium and comorbid delirium-dementia is a key diagnostic challenge. Development of new, efficient delirium-focused methods of cognitive assessment is a key challenge for improved detection of neurocognitive disorders in everyday clinical practice.

AIM

To compare the accuracy of two novel bedside tests of attention, vigilance and visuospatial function with conventional bedside cognitive tests in identifying delirium in older hospitalized patients.

METHODS

180 consecutive elderly medical inpatients (mean age 79.6 ± 7.2; 51% female) referred to a psychiatry for later life consultation-liaison service with delirium, dementia, comorbid delirium–dementia and cognitively intact controls. Participants were assessed cross-sectionally with conventional bedside cognitive tests [WORLD, Months Backward test (MBT), Spatial span, Vigilance A and B, Clock Drawing test and Interlocking Pentagons test] and two novel cognitive tests [Lighthouse test, Letter and Shape Drawing test (LSD)-4].

RESULTS

Neurocognitive diagnoses were delirium (n = 44), dementia (n = 30), comorbid delirium-dementia (n = 60) and no neurocognitive disorder (n = 46). All

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conventional tests had sensitivity of > 70% for delirium, with best overall accuracy for the Vigilance-B (78.3%), Vigilance-A (77.8%) and MBT (76.7%) tests. The sustained attention component of the Lighthouse test was the most distinguishing of delirium (sensitivity 84.6%; overall accuracy 75.6%). The LSD-4 had sensitivity of 74.0% and overall accuracy 74.4% for delirium identification. Combining tests allowed for enhanced sensitivity (> 90%) and overall accuracy (≥ 75%) with the highest overall accuracy for the combination of MBT-Vigilance A and the combined Vigilance A and B tests (both 78.3%). When analyses were repeated for those with dementia, there were similar findings with the MBT-Vigilance A the most accurate overall combination (80.0%). Combining the Lighthouse-SA with the LSD-4, a fail in either test had sensitivity for delirium of 91.4 with overall accuracy of 74.4%.

CONCLUSION
Bedside tests of attention, vigilance and visuospatial ability can help to distinguish neurocognitive disorders, including delirium, from other presentations. The Lighthouse test and the LSD-4 are novel tests with high accuracy for detecting delirium.

Key words: Visuospatial function; Attention; Vigilance; Letter and Shape Drawing test; Lighthouse test; Delirium; Dementia; Phenomenology; Assessment

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Core tip: This study examines the accuracy of a range of conventional and novel bedside cognitive tests in identifying delirium amongst older medical patients within a general hospital setting. The novel tests (Letter and Shape Drawing test, and Lighthouse test) compare favourably with conventional tests and may be particularly useful by virtue of their capacity to provide highly consistent testing in real world practice.

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INTRODUCTION

Major neurocognitive disorders are linked to a variety of adverse outcomes in hospitalized elderly[1,2]. However, these disorders are under-detected in everyday practice, leading to avoidable morbidity and mortality, rendering more accurate and timely recognition a key healthcare target[3,4]. A major obstacle to improved management of neurocognitive difficulties is the lack of clarity regarding optimal approaches to bedside cognitive assessment[5].

Recent studies exploring the phenomenological profile of major neurocognitive disorders suggest that tests of attention, vigilance and visuospatial abilities have particular utility in distinguishing neurocognitive disorders because these domains are disproportionately affected in delirium[6-10]. The results of such studies have the potential to lead to identification of a "cognitive vital sign" for routine and systematic assessment of cognition at the bedside in everyday practice.

Traditional or conventional bedside tests of cognition can assist in identifying delirium-relevant cognitive disturbances. However, these tests were developed in the last century and predate the modern concept of delirium that has been widely accepted since Diagnostic and Statistical Manual of Mental Disorders (DSM)-III in 1980[11]. Among their limitations for assessing for delirium are that they are subject to "bottoming-out" effects because they are too difficult for many patients, who cannot meaningfully engage with testing procedures[12]. Moreover, although these tests are widely used, there is major disparity in how they are administered and interpreted. For example, Meagher *et al*[13] found marked inconsistency in use of the Months Backward test (MBT) with almost no evidence of similar scoring of test performance

across 22 clinical studies. Similarly, a review of 16 studies of the Clock Drawing Test (CDT) in delirium identified 11 different scoring methods[14]. As such, more systematized and reliable methods of cognitive testing are needed, either based upon existing tests or by developing novel approaches to testing that draw upon modern (*e.g.*, computer-assisted/smartphone) technologies.

To this end, the Cognitive Impairment Research Group at the University of Limerick developed two novel tests specifically for the purpose of detecting cognitive difficulties that characterize delirium: The Lighthouse test, which focuses on attention/vigilance and the Letter and Shape Drawing test (LSD-4), which focuses upon visuospatial abilities[15-17]. This study the accuracy of a series of commonly used conventional tests as well as these novel tests in the detection of delirium in a real world sample of older hospital medical patients. Specifically, the aims were to (1) compare performance on these different tests in identifying delirium in elderly inpatients with varying neurocognitive disorder profiles as well as those with normal cognition; (2) examine how they compare (both individually and in combination) in terms of their specificity, sensitivity, positive and negative predictive value in detecting delirium and comorbid delirium-dementia in older medical inpatients; and (3) explore how accuracy is impacted upon by comorbid dementia.

MATERIALS AND METHODS

Subjects and design

A cross-sectional study of cognitive performance was conducted in referrals to a consultation-liaison psychiatry service of patients with delirium, dementia, comorbid delirium-dementia, as well as comparison subjects with no neurocognitive diagnosis (NNCD). Consecutive cases with altered mental state were identified on daily rounds by the medical team and referred for assessment and diagnosis by the research team.

Assessments were conducted by raters (Leonard M, Awan F, O'Connell H, Williams O, Meagher DJ) specifically trained in the use of the tests included herein (see below) and to further enhance inter-rater reliability, ratings associated with any uncertainty were discussed and agreed by consensus between raters.

Patients were assessed during the usual working day and in the majority of cases the process of receiving referrals and responding meant that this occurred in the early afternoon when the anchors of the day are thought to be optimally active. The assessments were conducted at the bedside to mimic real world practice.

Delirium was diagnosed according to a cut-off score of ≥ 15 on the severity scale of the Delirium Rating Scale-Revised-98 (DRS-R98)[18] and/or presence of DSM IV criteria[19] based upon a full clinical assessment. This approach was used because it allows for high diagnostic specificity in populations that include substantial numbers of patients with comorbid dementia. Dementia was defined as a clear history of documented DSM-IV[19] dementia (based on all available information at the time of assessment including clinical case notes and collateral history from family and/or carers) *or* a short Informant Questionnaire on Cognitive Decline in the elderly (IQCODE) score of ≥ 3.5[20]. Comorbid delirium-dementia was defined as the presence of both disorders.

Each subject was assessed with a battery of nine conventional (Rater A) and 2 novel (Rater B) tests (see below). Standard cut off performances were used to apply a binary (pass/fail) for each test where a fail corresponded with evidence of clinically significant impairment. Assessors were not aware of the patients' formal neurocognitive diagnoses. The cognitive tests were conducted in a fixed sequence as described below.

Informed consent

The procedures and rationale for the study were explained to all patients but because many patients had cognitive impairment at entry into the study it was presumed that many might not be capable of giving informed written consent. Because of the non-invasive nature of the study, University Hospital Limerick Regional Ethics Committee approved (REC 100/12) an approach to establishing consent by virtue of augmenting patient assent with proxy consent from next of kin (where possible) or a responsible caregiver for all participants in accordance with the Helsinki Guidelines for Medical Research involving human subjects[21].

Assessments

Demographic data and medication at the time of the assessment were recorded. All available information from medical records and collateral history was used. Nursing staff were interviewed to assist rating of symptoms over the previous 24 h.

The DRS-R98[18] is designed for broad phenomenological assessment of delirium. It is a 16-item scale with 13 severity and 3 diagnostic items with high interrater reliability, sensitivity and specificity for detecting delirium in mixed neuropsychiatric and other hospital populations. Each item is rated 0 (absent/normal) to 3 (severe impairment) with descriptions anchoring each severity level. Severity scale scores range from 0-39 with higher scores indicating more severe delirium. Delirium typically involves scores above 15 points (Severity scale) or 18 points (Total scale) when dementia is in the differential diagnosis.

The IQCODE-SF is a validated screening tool for detecting cognitive impairment. The short version of the IQCODE includes 16 items that rate cognitive change over time, each of which are rated by an informant on a 5 point Likert scale. The total score divided by the number of questions provides a mean item score where ratings ≥ 3.5 are considered indicative of longstanding cognitive difficulties and dementia[20].

Cognitive testing

WORLD backwards: The WORLD backwards test was applied according to the Mini–Mental State Examination[22]. Each participant was asked to spell WORLD backwards. Patients who self-corrected their own mistakes without prompting when spelling WORLD backwards were not penalized. Failure to correctly recite all five letters is considered to equate with clinically significant inattention (and thus a failed test).

MBT: In this test, the participant was asked to recite the months of the year in reverse order starting from December. Test duration was a maximum of 90 seconds at which point the subject's best performance was noted. Scoring in subjects over age 60 is that failure to reach July without more than one error of omission equates with clinically significant inattention (and thus a failed test)[13].

Spatial span forwards: This was conducted according to the description in the Cognitive test for delirium (CTD)[23]. The Spatial span forwards is a visual form of the digit span forwards. The subject is asked to copy the examiner in touching squares on a card (A5 size with 8 cm × 1 cm red squares). Each square represents a number and the test on each occasion requires that the squares corresponding to the digit span code are tapped at one second intervals. Two trials are conducted and the best performance is used. Failure to correctly complete a sequence of 5 or more numbers is considered to equate with clinically significant inattention (and thus a failed test).

Spatial span backwards: Similarly, the Spatial span backwards uses squares (blue) that are repeated in reverse order to that indicated by the assessor. Two trials are conducted and the best performance is used. Failure to correctly complete a sequence of three or more numbers is considered to equate with clinically significant inattention (and thus a failed test).This was also conducted according to the description in the original description of the CTD[23].

Vigilance A test: The vigilance "A" test was also derived from the CTD scale[23]. A list of 29 letters with the letter "A" included on 11 occasions was presented to the patient and they were asked to indicate each time the letter "A" was mentioned. Scores are calculated by subtracting commissions from correct responses (scored double) and rated as unable to engage with the test (0), score 1-9 (1), score 10-18 (2), score 19-26 (3), score > 27 (4). For the purposes of a binary (pass/fail) cutoff, we used failure to score > 27 to equate with significantly impaired vigilant (or sustained) attention.

Vigilance B test: This is similar to the vigilance A test except that there are two required letters ("C" and "E"). Scores are calculated by subtracting commissions from correct responses (scored double) and rated as unable to engage with the test (0), score 1-9 (1), score 10-18 (2), score 19-26 (3), score > 27 (4). For the purposes of a binary (pass/fail) cutoff, we used failure to score ≥ 19 to equate with significantly impaired vigilant (or sustained) attention[23].

Global assessment of visuospatial abilities: Visuospatial ability was rated according to a four point scale based upon DRS-R98 item 13[24] using both patient and collateral sources regarding ability to perceive differences in shape and distance as well as practical abilities such as navigating the ward environment and response to specific probes of describing how to get somewhere (*e.g*., bathroom), recognising shapes ("*what shape is the window*?") and differences in distances ("*which is closer the window or the hallway*?"). Patients with moderate or greater impairment in terms of responses to probes and/or reported need for redirection to keep from getting lost in the environment or difficulty locating familiar objects in immediate environment were considered to have pathological impairment of visuospatial abilities (failed test).

Intersecting Pentagons test: This geometric copying test is derived from the original Bender Gestalt test[25].The subject is presented with a copy of two intersecting pentagons drawn at angles to one another producing a diamond shape where they overlap. The subject is requested to copy the design on the blank half of the page. For scoring, we applied the six-point hierarchical scoring scale where 6 represents a perfect reproduction and 1 represents the poorest effort with scores < 4 equated with a failed performance[26].

CDT: The CDT examines visuospatial abilities as well as receptive language, numerical knowledge, working memory, and executive functions. It is widely used in geriatric practice as a cognitive scan. In this study, subjects were provided with a pre-drawn circle onto which the participant was requested to place all the numbers and the large and small hands on the clock face to show the time "ten past eleven". We used the scoring method of Sunderland *et al*[27] (1989) rating performance from 0 to 10 according to spatial representation of the numbers and hands of the clock. A score of < 6 equates with a failed performance.

LSD: The LSD is a novel test designed to emphasize visuospatial abilities[15]. It consists of a series of 4 designs that link 1cm spheres arranged in increasingly complex grids that the subject copies to an adjacent blank grid. The complexity ranges from very simple (copying an "X" on a 3 by 3 grid which is thought to assess awareness and basic understanding of the test procedures as well as physical ability to engage with testing) to increasingly more complex figures (*e.g*., on a 6 by 6 grid) designed to challenge those with higher levels of cognitive ability (Figure 1). A correct performance requires that all relevant spheres are connected to complete the required shape. Omissions (but not commissions) are rated as errors. Subjects are permitted a single trial of each of the 4 items. Each item is scored 0 or 1 depending on whether all target zones on the grid are completed, allowing for a total score ranging from 0-4. Scores less than 3 are considered to reflect clinically significant impairment of performance and equate with a failed performance[17].The test typically takes 1-2 min to complete. The test can be presented either as pen and paper or digitalised formats. The latter can allow for delivery of a more versatile test (that can be readily adapted to individual characteristics such as impaired visual or motor skills)[16]. The LSD thus provides a brief and easily interpreted bedside test of visuospatial function.

The Lighthouse test: The Lighthouse test was developed by the Cognitive Impairment Research Group as an objective assessment of awareness, focused and sustained attention. It is administered using an Android smartphone and involves presentation of an image of a flashing lighthouse on a standard screen (3" × 5")(Figure 2). The test has 3 main sections; (1) assessing whether the subject recognizes the lighthouse as such; (2) assessing the subject's capacity to focus attention to describe the number of times the lighthouse flashes (×3 sequences; 4, 3, 5). Subjects are requested to identify the number of flashes; and (3) testing the capacity to sustain attention to count sequences of flashes (×3) (*i.e*. 4-3-2, 3-2-5, 2-4-3) that last 12-15 seconds in duration. Again, subjects are requested to identify the total number of flashes.

Statistical analyses

Statistical analysis was conducted using SPSS-19[28]. Continuous data are presenting as means plus standard deviation. Categorical data are presented as counts and percentages. When multiple comparisons were conducted (ANOVA) the Bonferroni correction for multiple comparisons was used. The accuracy of tests of cognition (and their combinations), sensitivity and specificity as well as positive and negative likelihood ratio, Positive Predictive Value, and Negative Predictive Value were calculated, with confidence intervals testing significance at 95%. Post hoc power calculation for the main research question (the ability of LSD-4 to detect delirium against no delirium) was performed by using the G*Power v3.1.2. software. With a = 0.05, effect size = 0.5 and df = 3, a sample size of 180 indicated power of almost 1 (0.99).

RESULTS

A total of 180 patients were assessed [mean age 79.6 ± 7.2; 91 (51%) female]. The frequencies of neurocognitive diagnoses were; delirium (n = 44), dementia (n = 30), comorbid delirium-dementia (n = 60) and NNCD (n = 46). Demographic, medication and general clinical data for these four groups are shown in Table 1. There were no significant differences between the four groups in respect of age, gender distribution

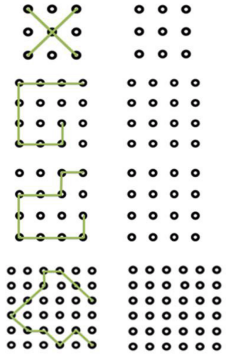


Figure 1 The Letter and Shape Drawing test.

or number of medications received, while psychotropic medication use was higher in those with any neurocognitive diagnosis.

Table 1 compares mean scores for the four groups for the DRS-R98 and IQ-CODE. Both delirium groups were more impaired than the dementia and NNCD groups on total scores for the DRS-R98. For the short IQCODE mean scores both dementia groups scored well above the suggested cut-off score and higher than the delirium-only and NNCD groups.

Table 2 and Table 3 show the performance on the conventional cognitive tests for the four neurocognitive groups, including accuracy for delirium diagnosis in the overall group as well as within the group with diagnosed dementia (n = 90) (Figure 3). Of note, all tests of attention and vigilance had a sensitivity for delirium of > 70% but, in terms of overall accuracy, the Vigilance A and B and MBT were the best performing tests. The tests of visuospatial ability were less sensitive to delirium, with the global assessment of visuospatial abilities (GVS) performing slightly better than the CDT and Intersecting Pentagons test (IPT).

Tables 4 and 5 show the performance on the three components of the Lighthouse test and the LSD-4. Overall, only one third of patients were able to identify the lighthouse correctly, with one third unable to describe it while the other third described it in a variety of ways including as "a lampost", "a traffic light", "a chimney" and "the Eiffel tower". The identification and focused attention components of the Lighthouse had substantially lower sensitivity and overall accuracy compared to the sustained attention (LH-SA) element and when combined with the LH-SA did not substantially add to its accuracy. The LH-SA alone compared favourably with the conventional tests of attention. Similarly, the LSD-4 compared favourably with the conventional tests of visuospatial abilities in terms of sensitivity and overall accuracy for detecting delirium, especially in those patients with dementia.

We examined the accuracy of various combinations of the conventional tests and the LH-SA/LSD in detecting delirium in the overall group and in the dementia group. The better performing combinations (*i.e*. those with sensitivity > 90% and overall accuracy ≥ 75%) are shown in Table 6. For the overall group, the MBT-GVS and the combined Vigilance A and B tests were the most sensitive combination (93.3%), while the MBT-Vigilance A and the combined Vigilance A and B tests had the highest overall accuracy (78.3%), with the LH-SA/LSD combination demonstrating similar levels of accuracy. When these analyses were repeated for the population with DSM-IV defined dementia, there were similar findings with the MBT-Vigilance A the most accurate overall combination (80.0%), followed by the LH-SA/LSD and combined Vigilance A and B tests (both 77.8%).

DISCUSSION

Performance on bedside tests of attention and visuospatial ability was compared in elderly medical inpatients with a variety of neurocognitive diagnoses and also with normal cognition. Participants were carefully diagnosed using a full neuropsychiatric assessment with well-validated instruments. Patients with active delirium (both with and without comorbid dementia) were distinguished from patients with dementia-alone in respect of performance on simple bedside tests. Moreover, combining tests of attention with visuospatial ability allowed for greater accuracy of delirium detection. Two novel cognitive tests, the LSD test both compare favourably with conventional tests and may offer advantages for use in everyday practice.



Figure 2 The Lighthouse test.

One important implication of this study is that formal testing using any conventional test can assist delirium detection – all tests were quite sensitive to the presence of delirium but the Vigilance A and B and the MBT were the best individual tests in terms of overall accuracy. This is in keeping with previous studies that have included direct comparisons of cognitive tests in the identification of delirium in elderly general hospital inpatients and which have consistently found that bedside tests of attention (including sustained or vigilant attention) are sensitive to the presence of delirium, with the Months Backward Test emerging as the most versatile individual test[10,29-33].

The Lighthouse is a novel test that includes three components designed to assess awareness/comprehension, focused attention and sustained attention. Somewhat surprisingly, only one third of subjects could correctly identify the Lighthouse thus, raising the possibility that the visual graphics are suboptimal. Although the ID and FA components did not individually add to the accuracy of the Lighthouse test for delirium, the testing procedures involved engaging with the stimulus and simple testing and may thus have optimised arousal and attention for the sustained attention component.

The LSD performed well in terms of delirium detection, demonstrating greater accuracy than the conventional visuospatial bedside tests (CDT and IPT), especially in those patients with dementia. Previous work has emphasised visuospatial function as a cognitive function that, along with attention, is particularly affected in delirium[6-10]. However, other work suggests that conventional tests such as the CDT lack specificity for delirium compared to dementia[14,32,34]. In contrast, the LSD which has been designed with the aim of optimising delirium-relevance, evidenced better specificity for delirium.

Efforts to identify optimal bedside cognitive testing for delirium monitoring should recognise that combining two tests that focus upon different aspects of cognition that are impaired in delirium can enhance accuracy of testing as well as inform delirium diagnosis which requires evidence of generalised disturbance to brain function. This should include impaired attention with deficits in at least one other cognitive domain[35] - visuospatial functioning offers a suitable second domain. In terms of accuracy, this work suggests that combining two tests can achieve > 90% sensitivity with high overall test accuracy. Combining the MBT with the Vigilance-A test is a particularly useful approach using conventional tests, while the combination of the LSD-4 with the sustained attention component of the Lighthouse test offers a novel approach that has similar accuracy. The latter has the advantage of being delivered by smartphone/tablet technology which can allow for enhanced consistency and reliability in test administration and interpretation. Moreover, digital technology offers the prospect of developing testing procedures that can be readily adapted according to individual patient characteristics such as visual acuity, frailty and motor dexterity – for example by altering the dimensions of presented material and/or the size of target zones on the LSD-4.

The LSD-4 and the Lighthouse are designed to emphasize consistency of administration and ease of interpretation. The methods applied in this study allowed for highly consistent administration procedures and detailed scoring systems that are not typically applied in everyday practice when using conventional bedside tests. Recent reviews[13,14] emphasize that conventional tools such as the MBT and the CDT are subject to considerable variability in use, with a lack of consensus as to optimal methods of administration and interpretation. As such, the accuracy of the conventional tests is likely to be lower in real world use. In contrast, the Lighthouse

Table 1 Demographic and clinical data for the total group and four neurocognitive groups (mean + SD)

	Total group (*n* = 180)	Delirium (*n* = 44)	Comorbid delirium-dementia (*n* = 60)	Dementia (*n* = 30)	No neurocognitive disorder (*n* = 46)
Female (%)	51%	53%	56%	37%	48%
Age	79.6 ± 7.2	77.7 ± 8.4	80.1 ± 7.0	81.8 ± 4.6	79.3 ± 7.5
Total number of medications	10.1 ± 4.7	10.0 ± 4.2	10.3 ± 5.0	9.7 ± 4.4	10.3 ± 5.1
Number of psychotropics[2]	1.7 ± 1.6	1.9 ± 1.6	2.2 ± 1.7	1.7 ± 1.6	0.8 ± 1.1
DRS-R98 total[12]	17.0 ± 9.2	22.9 ± 5.7	24.0 ± 6.0	10.9 ± 4.4	6.5 ± 3.3
Short IQCODE[3]	3.7 ± 0.7	3.1 ± 0.1	4.4 ± 0.5	4.0 ± 0.5	3.1 ± 0.1

[1]Delirium and comorbid delirium-dementia > dementia at $P < 0.001$.
[2]Delirium-only, dementia-only and comorbid delirium-dementia groups > no neurocognitive diagnosis (NNCD) at $P < 0.001$.
[3]Dementia and comorbid delirium-dementia groups > delirium and NNCD groups at $P < 0.001$. DRS-R98: Delirium Rating Scale-Revised-98; IQCODE: Informant Questionnaire on Cognitive Decline in the elderly.

test and the LSD-4 are more likely to maintain the accuracy evident herein due to their presentation in computerized format which enhances consistency of delivery and scoring and which may be associated with relatively less reduction in accuracy when used in everyday practice. In addition, we expect that the Lighthouse and LSD will be less subject to language-related inaccuracies than many other tests because they do not emphasize verbal skills. Future work can examine these issues, including the relative accuracy of computerized forms.

The combination of simple tests can allow for rapid and efficient assessment of delirium-relevant cognitive domains and achieved a sensitivity of almost 90% for delirium presence with these cross-sectional assessment methods. Serial monitoring of performance on these tests as a "cognitive vital sign" could allow for highly consistent detection of delirium in real world practice. Moreover, presentation in computerized formats could make for highly systematized assessment procedures that, given the modest specificity of 55%, would ideally be enhanced by a second phase of assessment for patients who identify as positive. This two-step approach to delirium detection is increasingly advocated as an effective means of improving detection rates in everyday clinical practice[5,36]. It is important to note that although identifying cognitive impairment is central to delirium diagnosis, actual diagnosis requires that the timing (relatively acute onset) and context (a deterioration from usual baseline, not better explained by another neuropsychiatric condition and due to a physical etiology) also be determined. Tools such as the confusion assessment method[37] and DRS-R98[18] incorporate these additional considerations to allow for formal diagnosis. Ultimately, systematized cognitive testing is key to delirium screening efforts and can also be used to support the cognitive assessment that is inherent to formal diagnosis. Psychometric data to guide the choice of test in particular settings is relatively lacking but ultimately the choice of cognitive testing tool is determined by a variety of factors that relate to patient, tester and other resource issues that are particular to the healthcare environment. Further work exploring the impact of these factors on the efficiency of providing cognitive-friendly healthcare is needed to guide choice of testing methods across settings.

Study limitations

This work has some notable shortcomings which include (1) We studied consecutive referrals to a consultation-liaison service for assessment of neuropsychiatric status. As such, these patients are likely to have a heightened symptom burden and are not representative of elderly inpatients in general; (2) We applied binary cut off ratings for each of the tests based upon best convention but for many tests a clear and consistently agreed pass/fail distinction is lacking; (3) We used a fixed order for presentation of the tests which may have influenced performance due to changing levels of arousal during the testing process and with the competing effects of practice versus fatigue[38]; and (4) We did not specify the stage or primary cause of dementia or take account of clinical subtypes of delirium (*i.e*. hypoactive, hyperactive and mixed motor subtype) although evidence indicates that neurocognitive disturbance varies across dementia types and severity[39].

Implications

Improved identification of major neurocognitive disorders is a key healthcare

Table 2 Performance on the Conventional bedside cognitive tests for the overall population and for each of the neurocognitive diagnostic groups (number completing correctly and %)

	Overall group (*n* = 180)	Delirium (*n* = 44)	Comorbid delirium-dementia (*n* = 60)	Dementia (*n* = 30)	NNCD (*n* = 46)
World backwards test	42 (23)	6 (14)	5 (8)	6 (20)	25 (54)
Months backwards test	74 (41)	12 (28)	8 (13)	20 (66)	34 (74)
Spatial span forwards	68 (38)	14 (32)	12 (20)	13 (43)	29 (63)
Spatial span backwards	67 (37)	15 (34)	8 (13)	15 (50)	29 (63)
Vigilance A test	88 (49)	16 (36)	10 (17)	23 (77)	39 (85)
Vigilance B test	49 (27)	3 (7)	3 (5)	13 (43)	30 (65)
Global visuospatial test	72 (40)	9 (20)	15 (25)	12 (40)	37 (80)
Clock drawing test	78 (43)	16 (36)	13 (22)	14 (47)	35 (76)
Interlocking pentagons test	87 (48)	17 (39)	14 (23)	18 (60)	38 (83)

NNCD: No neurocognitive diagnosis.

challenge. In particular, accurate and consistent detection of delirium is a priority because evidence indicates that more than half of cases are missed or detected late in everyday practice, with implications for morbidity, length of stay in hospital and mortality. A fundamental factor in enhancing recognition rates is to identify simple and brief methods for establishing the presence of clinically significant cognitive impairment at the bedside. Although both delirium and dementia involve generalised disturbance of cognitive function, delirium can be distinguished by virtue of the disproportionate impairment of attention and visuospatial ability. These cognitive domains can be readily assessed in everyday clinical practice using simple bedside tests. Both the Lighthouse and the LSD-4 provide accurate and delirium-oriented means of assessing cognitive function in delirium and in combination achieve a sensitivity of over 90% for delirium detection. Their impact upon delirium detection in everyday practice warrants further study as we seek to develop more efficient delirium monitoring in everyday practice.

Table 3 Accuracy of conventional bedside tests of cognition for delirium diagnosis in the overall population (*n* = 180) and for those with dementia (*n* = 90)

	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)	Overall accuracy (95%CI)
Overall population (*n* = 180)					
WORLD	89.4% (81.9–94.6)	40.8% (29.7–52.7)	67.4% (62.9-71.6)	73.8% (60.2-84.0)	68.9% (61.6-75.6)
MBT	80.8% (71.9-87.4)	71.1% (59.5-80.9)	79.3% (72.6-84.6)	73.0% (64.0-80.4)	76.7% (69.8-82.6)
SSF	75.0% (65.6-83.0)	55.3% (43.4-67.0)	69.6% (64.0-75.1)	61.8% (52.3-70.5)	66.7% (59.3-73.5)
SSB	77.9% (68.7-85.4)	57.9% (46.0-69.1)	71.7% (65.6-77.1)	65.7% (56.0-74.2)	69.4% (62.2-76.1)
Vigilance A	75.0% (65.6-83.0)	81.6% (71.0-89.6)	84.8% (77.4-90.1)	70.5% (62.7-77.2)	77.8% (71.0-83.6)
Vigilance B	94.2% (87.9-97.9)	56.6% (44.7-67.9)	74.8% (69.6-79.4)	87.8% (76.3-94.1)	78.3% (71.6-84.1)
GVS	76.9% (67.6-84.6)	63.2% (51.3-73.9)	74.1% (67.6-79.6)	66.7% (57.5-74.7)	71.1% (63.9-77.6)
CDT	72.1% (62.5-80.5)	64.5% (52.7-75.1)	73.5% (66.7-79.4)	62.8% (54.3-70.6)	68.9% (61.6-75.6)
IPT	70.2% (60.4-78.8)	73.7% (62.3-83.1)	78.5% (71.1-84.4)	64.4% (56.6-71.4)	71.7% (64.5-78.1)
Dementia population (*n* = 90)					
WORLD	91.7% (81.6-97.2)	20.0% (7.7-38.6)	69.6% (65.4-73.6)	54.6% (28.5-78.3)	67.8% (57.1-77.3)
MBT	86.7% (75.4-94.1)	66.7% (47.2-82.7)	83.9% (75.6-89.7)	71.4% (55.6-83.3)	80.0% (70.3-87.7)
SSF	80.0% (67.7-89.2)	43.3% (25.5-62.6)	73.9% (66.8-79.8)	52.0% (36.1-67.5)	67.8% (57.1-77.3)
SSB	86.7% (75.4-94.1)	50.0% (31.3-68.7)	77.6% (70.5-83.4)	65.2% (47.3-79.7)	74.4% (64.2-83.1)
Vigilance A	83.3% (71.5-91.7)	76.7% (57.7-90.1)	87.7% (78.1-93.2)	69.7% (55.8-80.7)	81.1% (71.5-88.6)
Vigilance B	95.0% (86.1-99.0)	43.3% (25.5-62.6)	77.0% (70.9-82.2)	81.3% (57.2-93.4)	77.8% (67.8-85.9)
GVS	75.0% (62.1-85.3)	40.0% (22.7-59.4)	71.4% (64.3-77.6)	44.4% (30.1-59.8)	63.3% (52.5-73.3)
CDT	78.3% (65.8-87.9)	46.7% (28.3 -65.7)	74.6% (67.2-80.8)	51.9% (36.8-66.6)	67.8% (57.1-77.3)
IPT	76.7% (64.0-86.6)	60.0% (40.6-77.3)	79.3% (70.8-85.9)	56.3% (42.7-68.9)	71.1% (60.6-80.2)

MBT: Months Backward test; SSF: Spatial span forwards; SSB: Spatial span backwards; GVS: Global assessment of visuospatial abilities; CDT: Clock Drawing test; IPT: Intersecting Pentagons test.

Table 4 Performance on Letter and Shape Drawing test and Lighthouse components (number completing correctly and %)

	Overall group (*n* = 180)	Delirium (*n* = 44)	Comorbid delirium-dementia (*n* = 60)	Dementia (*n* = 30)	NNCD (*n* = 46)
LH-identification	60 (33)	16 (36)	11 (18)	10 (33)	24 (52)
LH-FA	83 (46)	18 (41)	14 (23)	20 (66)	31 (67)
LH-SA	64 (36)	9 (21)	7 (12)	18 (60)	30 (65)
LSD	84 (48)	17 (39)	10 (17)	19 (63)	38 (83)

NNCD: No neurocognitive diagnosis; LSD: Letter and Shape Drawing test; LH: Lighthouse.

Table 5 Accuracy of Lighthouse components and Letter and Shape Drawing test for delirium diagnosis in the overall population (*n* = 180) and in those with dementia (*n* = 90)

	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)	Overall accuracy (95%CI)
Overall population (*n* = 180)					
LH-ID	74.0% (64.5-82.1)	44.7% (33.3-6.6)	64.7% (59.2-69.8)	55.7% (45.5- 65.5)	61.7% (54.1-68.8)
LH-FA	69.2% (59.4-77.9)	67.1% (55.4-77.5)	74.2% (67.1-80.3)	61.5% (53.4- 68.9)	68.3% (61.0-75.1)
LH-SA	84.6% (76.2-90.9)	63.2% (51.3-73.9)	75.9% (69.8-81.0)	75.0% (64.9-82.9)	75.6% (68.6-81.6)
LSD	74.0% (64.5-82.1)	75.0% (63.7-84.2)	80.2% (73.0-85.9)	67.9% (59.8-75.0)	74.4% (67.4-80.6)
Dementia population (*n* = 90)					
LH-ID	81.7% (69.6-90.5)	33.3% (17.3-52.8)	71.0% (64.9-76.4)	47.6% (30.3-65.5)	65.6% (54.8-75.3)

LH-FA	76.7% (64.0-86.6)	66.7% (47.2-82.7)	82.1% (73.1-88.6)	58.8% (45.8-70.7)	73.3% (63.0-82.1)
LH-SA	88.3% (77.4-95.2)	60.0% (40.6-77.3)	81.5% (73.8-87.4)	72.0% (54.7-84.6)	78.9% (69.0-86.8)
LSD	83.3% (71.5-91.7)	63.3 % (43.9-80.1)	82.0% (73.7-88.1)	65.5% (50.4- 78.1)	76.7% (66.6- 84.9)

LSD: Letter and Shape Drawing test; LH: Lighthouse.

Table 6 Most accurate combinations of conventional bedside tests and the combined sustained attention of Lighthouse/Letter and Shape Drawing Test

	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)	Overall accuracy (95%CI)
Overall population (*n* = 180)					
MBT plus GVS	93.3% (86.6-97.3)	48.7% (37.0-60.4)	71.3% (66.5-75.7)	84.1% (71.4-91.8)	74.4% (67.4-80.6)
Vig A plus GVS	92.3% (85.4-96.6)	57.9% (46.0-69.1)	75.0% (69.6-79.7)	84.6% (73.3-91.7)	77.8% (71.0-83.6)
Vig A plus Vig B	93.3% (86.6-97.3)	57.9% (46.0-69.1)	75.2% (69.9-79.9)	86.3% (75.0-93.0)	78.3% (71.6-84.1)
MBT plus Vig A	90.4% (83.0-95.3)	61.8 % (50.0-72.8)	76.4% (70.7-81.3)	82.5% (71.8- 89.7)	78.3% (71.6- 84.1)
LSD-4 plus Lighthouse-SA	91.4% (84.2-96.0)	51.3 % (39.6-63.0)	72.0 % (66.9-76.5)	81.3% (69.1-89.4)	74.4% (67.4-80.6)
Dementia population (*n* = 90)					
MBT plus GVS	93.3% (83.8-98.1)	30.0% (14.7-49.4)	72.7% (67.6-77.3)	69.2% 43.0-87.0)	72.2% (61.8-81.2)
Vig A plus GVS	95.0% (86.1-98.9)	33.3% (17.3- 52.8)	74.0% (68.7- 78.7)	76.9% (49.8-91.8)	74.4% (64.2- 83.1)
Vig A plus Vig B	95.0% (86.1-98.9)	43.3% (25.5-62.6)	77.0% (70.9-82.2)	81.3 (57.2-93.4)	77.8% (67.8-85.9)
MBT plus Vig A	95.0% (86.1-98.9)	50.0% (31.3-68.7)	79.2% (72.6-84.5)	83.3% (61.1-94.1)	80.0% (70.3-87.7)
LSD-4 plus LH-SA	95.0% (86.1-99.0)	43.3% (25.5-62.6)	77.0% (70.9-82.2)	81.3% (57.2-93.4)	77.8% (67.8-85.9)

MBT: Months Backward test; GVS: Global assessment of visuospatial abilities; CDT: Clock Drawing test; IPT: Intersecting Pentagons test; LH: Lighthouse; LSD: Letter and Shape Drawing test.

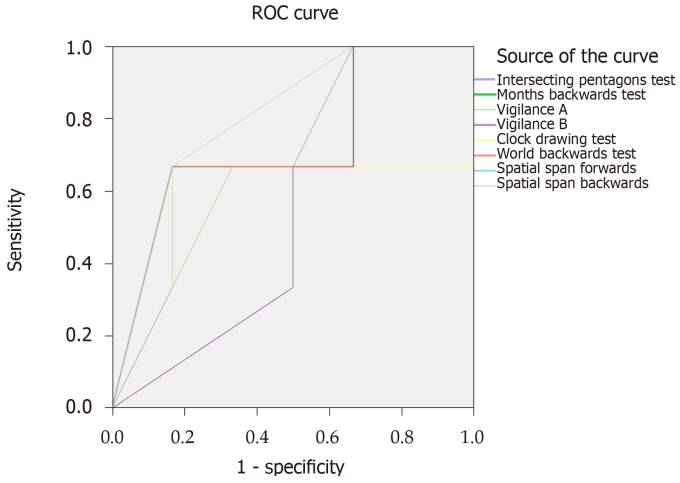


Figure 3 Receiver operating characteristic analyses depicting the accuracy of conventional bedside tests of cognition for delirium diagnosis in the overall population (*n* = 180). ROC: Receiver operating characteristic analyses.

ARTICLE HIGHLIGHTS

Research background

Efficient detection of delirium and comorbid delirium-dementia is a key diagnostic challenge. It's a key challenge of developing of new, efficient delirium-focused methods of cognitive assessment for improved detection of neurocognitive disorders in everyday clinical practice.

Research motivation

This study the accuracy of a series of commonly used conventional tests as well as these novel

tests in the detection of delirium in a real world sample of older hospital medical patients.

Research objectives
The authors aimed to compare the accuracy of two novel bedside tests of attention, vigilance and visuospatial function with conventional bedside cognitive tests in identifying delirium in older hospitalized patients.

Research methods
This cognitive performance study was conducted in referrals to a consultation-liaison psychiatry service of patients with delirium, dementia, comorbid delirium-dementia, as well as comparison subjects with no neurocognitive diagnosis. Altered mental state consecutive cases were identified on daily rounds.

Research results
All conventional tests had sensitivity of > 70% for delirium, with best overall accuracy for the Vigilance-B, Vigilance-A and Months Backward tests. The sustained attention component of the Lighthouse Test was the most distinguishing of delirium.

Research conclusions
Vigilance and visuospatial ability can help to distinguish neurocognitive disorders, including delirium, from other presentations. The Lighthouse test, Letter and Shape Drawing test are novel tests with high accuracy for detecting delirium.

Research perspectives
Lighthouse test, Letter and Shape Drawing tests' impact upon delirium detection in everyday practice warrants further study.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors for depression in patients with chronic obstructive pulmonary disease

Hui-Ming Yao, Ren-Sen Xiao, Ping-Liang Cao, Xiao-Lei Wang, Wei Zuo, Wei Zhang

ORCID number: Hui-Ming Yao (0000-0003-0067-2379); Ren-Sen Xiao (0000-0003-1358-2217); Ping-Liang Cao (0000-0002-1429-7752); Xiao-Lei Wang (0000-0002-9079-235X); Wei Zuo (0000-0003-2391-1678); Wei Zhang (0000-0002-6459-7614).

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Hui-Ming Yao, Ren-Sen Xiao, Wei Zuo, Wei Zhang, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

Ping-Liang Cao, Xiao-Lei Wang, Second Department of Cardiovascular Medicine, Jiangxi Provincial People's Hospital Affiliated to Nanchang University, Nanchang 330006, Jiangxi Province, China

Corresponding author: Wei Zhang, MD, PhD, Professor, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanchang University, No. 17 Yongwaizheng Street, Donghu District, Nanchang 330006, Jiangxi Province, China. weizhang1963@163.com

Abstract

BACKGROUND

The prevalence of depression in patients with chronic obstructive pulmonary disease (COPD) ranges from 10% to 42%, but the diagnosis of depression in patients with COPD is often unrecognized and untreated. Unrecognized depression has major implications for compliance with medical treatment, prolonged lengths of stay, increased frequency of hospital admissions, and increased consultations with primary care physicians. Many studies have attempted to identify risk factors for progression, prognosis and response to therapy in patients with depression. However, few studies have examined the risk factors for depression in patients with COPD, and some results remain controversial.

AIM

To identify the potential risk factors to define patients with COPD who are at "high risk" of depression.

METHODS

The clinical data of 293 patients with COPD were reviewed from January 2017 to December 2018. The correlations between demographics, clinical characteristics and depression were analyzed. The risk factors for depression in patients with COPD were identified by multivariate logistic regression analysis. The cutoff value, sensitivity and specificity of the independent correlation factors were calculated with a receiver operating characteristic curve.

RESULTS

Of the 293 patients included, 65 (22.18%) individuals were identified to have

additional data are available.

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depression. Significant differences were detected between patients with and without depression in terms of body mass index (BMI), forced expiratory volume in 1 s (FEV1), and COPD assessment test (CAT) score (all $P < 0.05$). Low BMI, low FEV1, and high CAT were independent risk factors for depression in patients with COPD and the cutoff values of BMI, FEV1, and CAT scores were 21.373 kg/m^2, 0.855 L and 12.5, respectively.

CONCLUSION
Low BMI, low FEV1, and high CAT score were identified as independent risk factors for depression in patients with COPD.

Key words: Depression; Chronic obstructive pulmonary disease; Body mass index; Forced expiratory volume in 1 second; Chronic obstructive pulmonary disease assessment test scores; Risk factors

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Core tip: The prevalence of depression in patients with chronic obstructive pulmonary disease (COPD) ranges from 10% to 42%. However, the risk factors for depression in patients with COPD have been examined in few studies, and some results remain controversial. The purpose of the current study is to investigate the correlation between clinical parameters and the symptoms of depression, and to identify independent risk factors to define patients with COPD who are at "high risk" of depression. Low body mass index, low forced expiratory volume in 1 s and high chronic obstructive pulmonary disease assessment test score were identified as independent risk factors for depression in patients with COPD.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity with an economic and social burden that is both substantial and increasing[1,2]. COPD is currently the fourth-leading cause of death and is expected to surpass stroke within the next decade to become the third leading cause of death[3]. Because medical treatments have made limited inroads, patients with COPD experience recurring acute exacerbations, frequent hospital admissions, poor survival, and impaired physical functioning and quality of life[4-6]. The reported prevalence of depression in patients with COPD ranges from 10% to 42%, a proportion much higher than that in the general population[7,8]. Although evidence suggests that certain interventions such as antidepressants, pulmonary rehabilitation, and counseling may improve health outcomes, the diagnosis of depression in patients with COPD is often unrecognized and untreated in primary and specialty care[9,10]. Unrecognized depression has major implications for compliance with medical treatment, prolonged lengths of stay, increased frequency of hospital admissions, and increased consultations with primary care physicians, all of which could decrease quality of life in patients[11,12]. The Hospital Anxiety and Depression Rating Scale (HADS) is one of the most commonly used instruments for depression in the literature[13]. The HADS is subjective and is intended for anxiety and depression screening of patients in general hospitals. It is a 14-item self-report questionnaire comprising two subscales: HADS-anxiety subscale (HADS-A) and HADS-depression subscale (HADS-D), which are scored from 0 to 21 to detect the presence of symptoms of anxiety and depression. The scale is designed for use in patients with physical illness; therefore, none of the items include somatic symptoms of depression or anxiety. Although the screening tool is widely available, it cannot provide enough information for early diagnosis.

Many studies have attempted to identify risk factors for progression, prognosis and response to therapy in patients with depression[10,14]. However, few studies have

examined the risk factors for depression in patients with COPD, and some results remain controversial[14]. Thus, further research is needed to detect depression in patients with COPD for early diagnosis and treatment. The purpose of the current study is to investigate the correlation between clinical parameters and the symptoms of depression, and to identify independent risk factors to define patients with COPD at "high risk" of depression.

MATERIALS AND METHODS

Patients

This was a retrospective study with no involvement in clinical or animal research. The requirement for ethical permission was waived according to the statements regarding the application of ethical permission by the Ethical Committee of the First Affiliated Hospital of Nanchang University. A retrospective study was conducted and a series of consecutive patients newly diagnosed with COPD between January 2017 and December 2018 were included in this study. COPD diagnosis was made according to the Global Initiative for Chronic Obstructive Lung Disease[15]. We studied the files of the patients carefully to ensure that all factors that might affect the outcome of the assessment were considered when the patients were included in this study. Standard treatment was given to each patient. The diagnosis of depression mainly relied on the HADS-D, and the HADS scale was carried out by an experienced psychiatrist when the patients were stable. A review and meta-analysis of studies reported that a cutoff of 8 or more on the HADS-D produced a sensitivity of 0.82 (95%CI: 0.73–80) and a specificity of 0.74 (95%CI: 0.60–0.84) for depressive disorders[16]. Therefore, we used a cutoff of 8 or more on the HADS-D to dichotomize the HADS-D scores for the purposes of the regression analyses. All the patients were inpatients and were recruited from medical hospital wards.

Patients presenting with confounders of comorbidity or other conditions that could potentially affect the evaluation of risk factors, such as dependent care living situations, life expectancy of less than six months, trouble with eye-sight, and diagnosis of dementia or Alzheimer's disease, were excluded from this study. For patients already diagnosed with depressive disorder or history of such disorder, only those with depression associated with COPD were included in this study and the judgments were made by an experienced psychiatrist. Patients receiving antidepressants, anxiolytics or other psychiatric medication were excluded in order to avoid introducing bias as treatment options might have a potential impact on HADS scores.

Data collection

The demographics and clinical characteristics of the patients in this retrospective study included age, gender, marital status, household income, smoking status, duration of respiratory symptoms, number of acute exacerbations in the previous year, body mass index (BMI, kg/m^2), forced expiratory volume in 1 s (FEV1, L), and Modified British Medical Research Council Questionnaire (mMRC) and Chronic Obstructive Pulmonary Disease assessment test (CAT) scores at the time of the primary diagnosis of COPD. The correlation between clinical parameters and depression was analyzed, and the risk factors for depression in patients with COPD were identified.

Statistical analysis

All analyses were performed using IBM SPSS Version 22 (SPSS Inc. Chicago IL, USA). Qualitative variables were expressed as numbers and percentages, and were assessed by the χ^2 test or Fisher's exact test. Continuous variables were reported as the mean ± SD and were compared with independent samples *t*-tests or univariate analysis. Independent risk factors related to depression were analyzed using a multivariate logistic regression analysis model. A receiver operating characteristic (ROC) curve was used to assess the predictive value of risk factors in patients with depression. Statistical significance was set as a *P* value less than 0.05.

RESULTS

Patient demographics

A total of 293 patients with COPD were included in this study (Figure 1). Patients' demographics are shown in Table 1. Of the 293 patients who were eligible for inclusion, 65 individuals were identified to have depression. The overall incidence of

depression in this study was 22.18% (65/293). Most of the patients were male (240 patients, 81.91%), with an average age of 65.62 ± 7.31 years. Among these patients, 38.91% were past smokers, and 33.79% were current smokers. The household income type of most patients was low income (149 patients, 50.85%) or medium income (105 patients, 35.84%).

The correlation between diverse clinical factors and depression

The differences between clinical parameters and depression were investigated and the results are presented in Table 2. The results revealed that depression in patients with COPD was associated with the duration of respiratory symptoms, the number of exacerbations per year, BMI, FEV1, and the mMRC dyspnea scale and CAT scores as significant differences were found between patients with and without depression for these factors (all $P < 0.05$). These results indicated that the duration of respiratory symptoms, the number of exacerbations per year, BMI, FEV1, and the mMRC dyspnea scale and CAT scores were potentially related to depression in patients with COPD. No statistically significant differences in age, gender, marital status, household income and smoking history were observed between the 2 groups ($P > 0.05$).

Risk factors for depression in patients with COPD

Multivariate logistic regression analysis was carried out to identify the potential risk factors for depression in patients with COPD. Low BMI (OR = 0.893, $P < 0.05$), low FEV1 (OR = 0.325, $P < 0.05$), and high CAT score (OR = 1.111, $P < 0.05$) were independent risk factors for depression. No significant differences were found for the duration of respiratory symptoms or the number of exacerbations per year between COPD patients with and without depression ($P > 0.05$) (Table 3).

The cutoff value, sensitivity, and specificity of BMI, FEV1, and CAT score for diagnosing depression

Figure 2, Figure 3 and Figure 4 show the ROC curves of BMI, FEV1, and CAT score for predicting the risk of depression; these factors had comparable accuracy in predicting depression in COPD patients (the AUC of these factors were 0.705, 0.702 and 0.694, respectively). The cutoff values of these factors were 21.375 kg/m^2, 0.855 L and 12.5, respectively. BMI had the highest diagnostic accuracy for predicting the risk of depression (AUC = 0.705, $P < 0.05$), with a sensitivity and specificity of 49.6% and 83.1%, respectively. Additionally, combined BMI and FEV1 with CAT score had a higher AUC (BMI + FEV1: 74.5%; BMI + CAT: 73.5%; FEV1 + CAT: 73.0%; BMI + FEV1 + CAT: 76.6%) than that of one single factor (Table 4).

DISCUSSION

COPD is a major respiratory noncommunicable disease and is currently the third leading cause of death worldwide[17]. Depression occurs in up to 42% of persons with COPD[11], almost twice as often as in those without COPD[18]. In line with previous studies, the incidence of depression in our study was 22.18%, based on a population of 293 patients. Depression in patients with COPD is associated with physical impairment[19], readmission[20], increased dyspnea[21,22], and mortality[23]. Due to the considerable overlap between the physical symptoms of depression and the symptoms of COPD, patients with COPD may not be able to recognize this mental illness, and diagnosis is easily missed by doctors compared with that in patients with other comorbidities or depression alone[24]. Due to these factors, depression may reduce patient compliance with COPD treatment, thus leading to deterioration related to COPD. Therefore, identifying valuable predictive factors that are readily available could meaningfully benefit timely intervention to cure depression. In this retrospective study, we evaluated the association between clinical factors and depression in patients with COPD. Previous studies reported that depression in patients with COPD was associated with multiple factors, including age, gender, marital status, smoking history and social performance[25-27]. However, in this study, a correlation between the above-mentioned factors and depression was not found. The reason for this result may be that these studies were performed primarily in patients with severe COPD, and few of them focused on risk factors in patients with mild COPD.

BMI had been widely used to measure obesity, and there is growing evidence that BMI is an independent predictor of mental disorders[28]. A previous study reported that the average depression score in an obesity group was higher than that in a normal BMI group[28]. Zhao *et al*[29] revealed that obese individuals (≥ 25.0 kg/m^2) were 38% more likely to experience depression, and were 40% more likely to have lifetime depression after fully adjusting for several factors, such as obesity-related

Table 1 Baseline characteristics of patients, *n* = 293 (%)

Patient characteristics	Number of patients
Age at diagnosis (mean ± SD, yr)	65.62 ± 7.31
Gender	
Female	53 (18.09)
Male	240 (81.91)
Smoking history	
Never smoker	80 (27.30)
Past smoker	114 (38.91)
Current smoker	99 (33.79)
Household income	
Low income	149 (50.85)
Medium income	105 (35.84)
High income	39 (13.31)
Patients with depression	65 (22.18)
HADS-D score	5.09 ± 2.73

HADS-D: Hospital anxiety and depression scale-depression.

comorbidities, demographics, and psychosocial factors. Lee *et al*[30] indicated that adjusted odds ratios for depression formed a U-shaped relationship with BMI categories (underweight group: 1.31, overweight group: 0.94, obese group: 1.01, severely obese group: 1.28). The BMI level with the lowest likelihood of depression was 18.5-25 kg/m^2 in women and 23-25 kg/m^2 in men[30]. However, few studies have analyzed the relationship between BMI and depression in patients with COPD. In the current study, we identified BMI as an independent risk factor correlated with depression. The cutoff value was 21.375 kg/m^2. This finding suggested that BMI levels < 21.375 kg/m^2 could help to distinguish populations of patients with COPD at a higher risk of depression.

Previous data highlighted the association between FEV1 and depression. A study reported that among 100 dairy farmers with COPD, as defined by a postbronchodilator FEV1/forced vital capacity ratio < 0.7, depression in patients was associated with lower FEV1, as well as with certain COPD-related characteristics (current smoking, dyspnea severity, and poorer quality of life)[31]. Von Siemens *et al*[32] demonstrated that FEV1 was significantly (P < 0.05) related to the Patient Health Questionnaire 9 score, which is one of the screening tools for depression. Significant differences were found for FEV1 levels, reflecting COPD severity, between patients with and without depression[33]. This result could help patients with depression avoid being untreated or undertreated[34]. Consistent with previous studies, our study indicated that FEV1 was an independent risk factor for depression in patients with COPD. The cut-off value was 0.855 L, and the sensitivity and specificity were 71.5% and 63.1%, respectively.

The CAT score was developed in 2009 as a patient-administered, short questionnaire to test health-related quality of life in patients with COPD[35]. Lower scores indicated less severe symptoms. There was a significant difference in CAT scores between patients with depression and without depression[35]. The analyses by von Siemens *et al*[32] revealed, with a cut-off CAT score of 20, an AUC of 0.81. Based on the close relationship between the tests, the CAT score and depression were also omitted from further analysis. Interestingly, this value was similar to the critical value of 18, which had been proposed to be better than the conventional threshold of 10 in terms of the classification of COPD severity. Lee *et al*[36] indicated that the CAT score and symptoms were correlated with the formation of depression in patients with COPD. In line with previous studies, the results of our study showed significant differences in CAT scores between patients with and without depression, and we identified that the CAT score was an independent risk factor correlated with depression. The cutoff value was 12.5. This finding indicated that a CAT score > 12.5 was a risk factor for depression in patients with COPD.

To identify the predictive accuracy of combined risk factors for predicting depression in patients with COPD, we analyzed the combined risk factors for depression in the present study. Compared to BMI, FEV1 or CAT score alone, we found that combining FEV1 and CAT score with BMI had higher predictive value for predicting depression in patients with COPD. This finding indicated that the

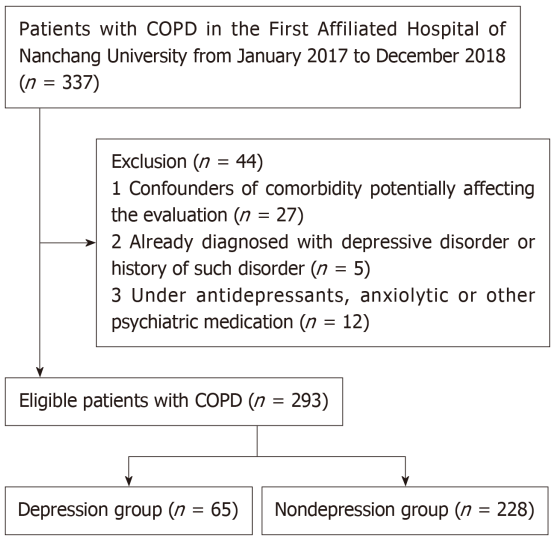


Figure 1 Selection of the study participants. COPD: Chronic obstructive pulmonary disease.

combination of risk factors appeared to be more useful for predicting depression.

To our knowledge, we have been successful in identifying low BMI, low FEV1 and high CAT score as independent depression associated risk factors in patients with COPD. Although the results are interesting, limitations to our study still exist. First, this was a retrospective study with a relatively small sample, which may have resulted in bias during analysis of the results. Second, we only collected variables from patients with COPD at the time of diagnosis, and some variables, such as the time to depression and follow up, were not reported. Third, patient variables were from a single medical institution and the results of our study for predicting depression were not satisfactory. Thus, a multicenter study with more patients is needed to verify our results. Fourth, some studies indicated that the HADS was saturated by the presence of a common distressing factor, in part because it was intended to focus on lack of pleasure and autonomous arousal, leading to the difficulty in distinguishing depression from anxiety. This explained the result that the HADS anxiety scale and depression scale served the same purpose as a screening tool for depression[37]. For research purposes, the use of a summed HADS total score was recommended and appeared to provide an adequate estimate. In clinical practice, HADS is not recommended when it is necessary to distinguish between anxiety and depression. Due to its poor trait coverage and narrow focus, short tools covering broad anxiety and depression symptoms may be more appropriate[38,39]. COPD patients have greater disease burden than other populations. In addition to the widespread symptoms of depression, our results also identified several risk factors for depression including low BMI, low FEV1, and high CAT score. However, barriers to recognition exist at the provider and system levels. At the provider level, lack of ambitions and stereotypes can be obstacles. At the system level, poor integration of mental health services with primary health care is another obstacle.

In conclusion, based on this analysis, we established that approximately one-fifth of patients with COPD developed depression. Additionally, we identified low BMI, low FEV1, and high CAT score as risk factors for depression in COPD patients. Combining these factors predicted the highest risk of developing depression. However, a prospective study with a large sample size and multicenter analysis is needed to prove the conclusions of our study.

Table 2 Correlation between diverse clinical factors and depression

Factors	Depression	No depression	*P* value
Age at diagnosis (mean ± SD, yr)	65.12 ± 7.62	65.76 ± 7.23	NS
Gender	65	228	NS
Female	9	44	
Male	56	184	
Marital status	65	228	NS
Married or partner	52	194	
Single, divorced, separated or widowed	13	34	
Household income	65	228	NS
High income	12	27	
Medium income	20	82	
Low income	33	119	
Smoking history	65	228	NS
Never smoker	15	49	
Past smoker	24	96	
Current smoker	26	83	
Duration of respiratory symptoms (mo)	111.28 ± 41.92	79.51 ± 112.47	0.026
Exacerbation rate (prior yr)	2.09 ± 1.28	1.58 ± 0.94	0.004
BMI (kg/m^2)	18.51 ± 3.34	20.75 ± 4.09	0.000
FEV1 (L)	0.82 ± 0.30	1.11 ± 0.44	0.000
mMRC dyspnea scale	1.86 ± 0.75	1.67 ± 0.69	NS
CAT score	13.08 ± 3.71	10.30 ± 4.20	0.002
HADS score	9.18 ± 1.27	3.93 ± 1.72	0.000

BMI: Body mass index; FEV1: Forced expiratory volume in 1 s; mMRC: Modified medical research council; CAT: Chronic obstructive pulmonary disease assessment test; HADS: Hospital Anxiety and Depression Rating Scale; NS: Not significant.

Table 3 Multivariate logistic regression analysis of risk factors

Factors	β	OR	95%CI	*P* value
Duration of respiratory symptoms	0.002	1.002	0.999-1.004	NS
Exacerbation rate (prior yr)	0.13	1.139	0.854-1.518	NS
BMI (kg/m^2)	-0.113	0.893	0.830-0.962	0.003
FEV1 (L)	-1.124	0.325	0.132-0.803	0.002
CAT score	0.105	1.111	1.021-1.209	0.004

β: Coefficient regression; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; FEV1: Forced expiratory volume in 1 s; CAT: Chronic obstructive pulmonary disease assessment test; NS: Not significant.

Table 4 Cutoff value, sensitivity, and specificity of body mass index, forced expiratory volume in 1 s, and chronic obstructive pulmonary disease assessment test score for diagnosing depression

Factors	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	95%CI	*P* value
BMI (kg/m^2)	21.375	49.6	83.1	0.705	0.633-0.776	0.001
FEV1 (L)	0.855	71.5	63.1	0.702	0.634-0.770	0.003
CAT score	12.5	63.1	70.6	0.694	0.624-0.765	0.001
BMI+FEV1		76.9	66.7	0.745	0.684-0.807	0.000
BMI+CAT		72.3	67.1	0.735	0.669-0.802	0.000
FEV1+CAT		76.9	60.5	0.730	0.667-0.794	0.000
BMI+FEV1+CAT		72.3	75.0	0.766	0.705-0.827	0.000

BMI: Body mass index; FEV1: Forced expiratory volume in 1 s; CAT: Chronic obstructive pulmonary disease assessment test; AUC: Area under curve; CI: Confidence interval.

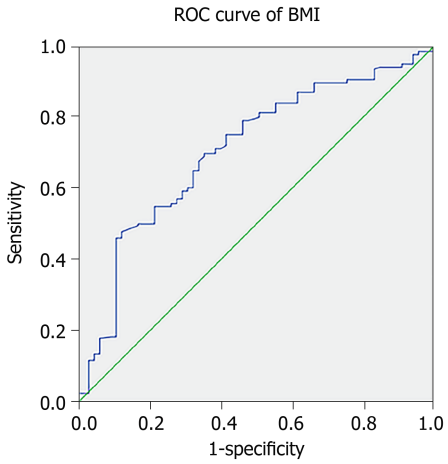


Figure 2 Receiver operating characteristic curve of body mass index. The receiver operating characteristic curve demonstrated the sensitivities and specificities of body mass index for predicting the risk of depression in patients with chronic obstructive pulmonary disease. ROC curve: Receiver operating characteristic curve; BMI: Body mass index.

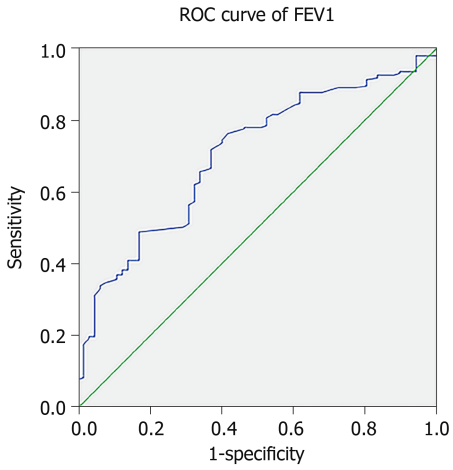


Figure 3 Receiver operating characteristic curve of forced expiratory volume in 1 s. The receiver operating characteristic curve demonstrated the sensitivities and specificities of forced expiratory volume in 1 s for predicting the risk of depression in patients with chronic obstructive pulmonary disease. ROC curve: Receiver operating characteristic curve; FEV1: Forced expiratory volume in 1 s.

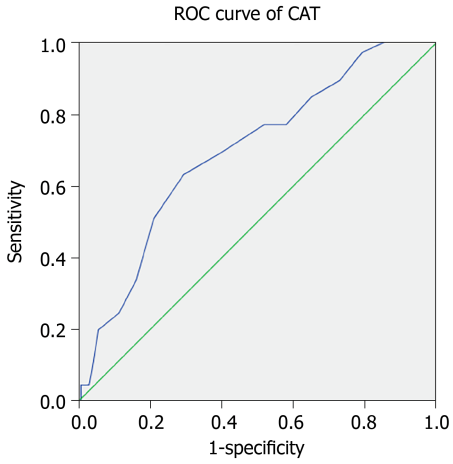


Figure 4 Receiver operating characteristic curve of chronic obstructive pulmonary disease assessment test score. The receiver operating characteristic curve demonstrated the sensitivities and specificities of the chronic obstructive pulmonary disease assessment test score for predicting the risk of depression in patients with chronic obstructive pulmonary disease. ROC curve: Receiver operating characteristic curve; CAT: Chronic obstructive pulmonary disease assessment test.

ARTICLE HIGHLIGHTS

Research background

The reported prevalence of depression in patients with chronic obstructive pulmonary disease (COPD) ranges from 10% to 42%, a proportion much higher than that in the general population. Certain interventions such as antidepressants, pulmonary rehabilitation, and counseling may improve health outcomes, but the diagnosis of depression in patients with COPD is often unrecognized and untreated in primary and specialty care. Unrecognized depression has major implications for compliance with medical treatment, prolonged lengths of stay, increased frequency of hospital admissions, and increased consultations with primary care physicians, all of which could decrease quality of life in patients.

Research motivation

Many studies have attempted to identify risk factors for progression, prognosis and response to therapy in patients with depression. However, few studies have examined the risk factors for depression in patients with COPD, and some results remain controversial.

Research objectives

The main objective of the current study is to investigate the correlation between clinical parameters and the symptoms of depression, and to identify independent risk factors to define patients with COPD at "high risk" of depression.

Research methods

The Hospital Anxiety and Depression Rating Scale (HADS) is one of the most commonly used instruments for depression in the literature. A series of consecutive patients newly diagnosed with COPD were included in this study. The diagnosis of depression mainly relied on the HADS, and the HADS scale was carried out by an experienced psychiatrist when the patients were stable. We used a cutoff of 8 or more on the HADS to dichotomize the HADS scores for the purposes of the regression analyses. The correlation between clinical parameters and depression was analyzed, and the risk factors for depression in patients with COPD were identified.

Research results

Multivariate logistic regression analysis was carried out to identify the potential risk factors for depression in patients with COPD. Low body mass index (BMI), low forced expiratory volume in 1 s (FEV1), and high COPD assessment test (CAT) score were independent risk factors for depression. BMI had the highest diagnostic accuracy for predicting the risk of depression. Additionally, combined BMI and FEV1 with CAT score had a higher area under curve than that of one single factor.

Research conclusions

Approximately one-fifth of patients with COPD developed depression. Additionally, we identified low BMI, low FEV1, and high CAT score as risk factors for depression in COPD patients. Combining these factors predicted the highest risk of developing depression.

Research perspectives

Some variables, such as the time to depression and follow up, were not reported, which may have resulted in bias during analysis of the results. A prospective study with a large sample size and multicenter analysis is needed to prove the conclusions of our study.

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META-ANALYSIS

Diagnostic accuracy and clinical utility of non-English versions of Edinburgh Post-Natal Depression Scale for screening post-natal depression in India: A meta-analysis

Paul Swamidhas Sudhakar Russell, Swetha Madhuri Chikkala, Richa Earnest, Shonima Aynipully Viswanathan, Sushila Russell, Priya Mary Mammen

ORCID number: Paul Swamidhas Sudhakar Russell (0000-0001-6463-2750); Swetha Madhuri Chikkala (0000-0002-1462-1751); Richa Earnest (0000-0002-1701-8392); Shonima Aynipully Viswanathan (0000-0002-3792-0009); Sushila Russell (0000-0003-0055-1542); Priya Mary Mammen (0000-0001-7182-6959).

Author contributions: Russell PSS and Chikkala SW contributed equally to this work; Russell PSS and Chikkala SM conceived and designed the study; Chikkala SM and Earnest R did the literature search and collected data; Russell S and Viswanathan SA extracted the data; Viswanathan SA and Mammen PM appraised the quality of the studies; Russell PSS resolved the conflicts in data synthesis; Russell PSS did the statistical analyses; all authors contributed to the writing and approval of the manuscript.

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Paul Swamidhas Sudhakar Russell, Swetha Madhuri Chikkala, Richa Earnest, Shonima Aynipully Viswanathan, Sushila Russell, Priya Mary Mammen, Child and Adolescent Psychiatry Unit, Department of Psychiatry, Christian Medical College, Vellore 632 002, India

Corresponding author: Paul Swamidhas Sudhakar Russell, MBBS, MD, Professor, Child and Adolescent Psychiatry Unit, Department of Psychiatry, Christian Medical College, Bagayam, Vellore 632 002, India. russell@cmcvellore.ac.in

Abstract

BACKGROUND

The prevalence of post-natal depression (PND) is high in India, as it is in many other low to middle income countries. There is an urgent need to identify PND and treat the mother as early as possible. Among the many paper and pencil tests available to identify PND, the Edinburgh Postnatal Depression Scale (EPDS) is a widely used and validated measure in India. However, the summary diagnostic accuracy and clinical utility data are not available for this measure.

AIM

To establish summary data for the global diagnostic accuracy parameter as well as the clinical utility of the non-English versions of the EPDS in India.

METHODS

Two researchers independently searched the PubMed, EMBASE, MEDKNOW and IndMED databases for published papers, governmental publications, conference proceedings and grey literature from 2000-2018. Seven studies that evaluated the diagnostic accuracy of EPDS in five Indian languages against DSM/ICD were included in the final analysis. Two other investigators extracted the Participants' details, Index measures, Comparative reference measures, and Outcomes of diagnostic accuracy data, and appraised the study quality using QUADS-2. Deek's plots were used to evaluate publication bias. We used the area under the curve of the hierarchical summary area under the receiver operating characteristic curve, with the random effect model, to summarize the global diagnostic accuracy of EPDS. Using the 2 × 2 table, we calculated positive and negative likelihood ratios. From the likelihood ratios, the Fagan's nomogram was built for evaluating clinical utility using the Bayesian approach. We calculated the 95% confidence interval (95%CI) whenever indicated. STATA (version 15) with MIDAS and METANDI modules were used.

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RESULTS

There was no publication bias. The area under the curve for EPDS was 0.97 (95%CI: 0.95-0.98). The pre-test probability for the nomogram was 22%. For a positive likelihood ratio of 9, the positive post-test probability was 72% (95%CI: 68%, 76%) and for a negative LR of 0.08, the negative post-test probability was 2% (95%CI: 1%, 3%).

CONCLUSION

In this meta-analysis, we established the summary global diagnostic parameter and clinical utility of the non-English versions of the EPDS in India. This work demonstrates that these non-English versions are accurate in their diagnosis of PND and can help clinicians in their diagnostic reasoning.

Key words: Clinical-utility; Diagnostic-accuracy; Edinburgh Postnatal Depression Scale; Meta-analysis; India; Validation

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Core tip: Post-natal depression (PND) affects both the mother and baby. Currently, although one of the most common psychiatric disorders among women, early identification and treatment is underprovided in low and middle-income countries. Paper-and-pencil tests remain the primary mode of identifying PND, and the Edinburgh Postnatal Depression Scale is widely used and validated in many languages in India. This meta-analysis documents that the diagnostic parameters are good for Edinburgh Postnatal Depression Scale in India, and that its use can significantly help to scale up the services for PND.

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INTRODUCTION

India is a low-middle income country with a birth rate of 20/1000 population, and the summary prevalence of Post-natal Depression (PND) was 22% in the country in 2017[1-3]. There is compelling evidence that PND is associated with morbidity and mortality in the mother-infant dyad[4,5]. Therefore, scaling-up identification and early, effective management of the identified mother-infant dyad is very much needed in India.

The Edinburgh Postnatal Depression Scale (EPDS) is an accurate screening measure[6,7] and improves the follow-up care of PND and maternal mental health[8]. In India, it is the most commonly used screening measure for PND. A recent meta-analysis demonstrates that 29 of the 38 prevalence studies on PND have used EPDS in India[3]. This measure has been translated and validated in the eight regional languages of India: Assamese, Bengali, Gujarati, Kannada, Konkani, Marathi, Punjabi and Tamil, and has been validated in both clinical and community settings in India against a variety of reference standards. The total EPDS threshold score for diagnosing PND has ranged from 6/7 to 12.5/13. Reflecting the possible effect of the varying prevalence of PND, the setting of the study, the threshold-score of EPDS, and the reference standard used or other methodological differences, the sensitivity and specificity have varied from 71%-100% and 77%-98%, respectively (further details are given in Table 1). Furthermore, good diagnostic accuracy does not always translate into good clinical utility among measures. The clinical utility of EPDS has not previously been studied in India. Therefore, because of the wide variation in diagnostic accuracy parameters, there is a need to generate summary diagnostic accuracy parameters from pooled studies for use across India, and its clinical utility needs to be demonstrated.

Using this meta-analysis, we aim to fill in the lacunae in the existing literature,

Table 1 Summary of the included and excluded studies with their individual Quality Assessment of Diagnostic-Accuracy Studies-2 details

PICO details								QUADAS-2						
								Risk of bias				Applicability concerns		
Ref.	Sample, *n*	Setting, Age, PN	EPDS language	EPDS threshold	Interview schedule, Reference standard	Sn	Sp	PS	IT	RS	F&T	PS	IT	RS
Patel *et al*[13], 2002	270	Clinic, 18-40 yr, 6-8 wk PN	Konkani	11/12	CIS-R, ICD-10	92	85	UC	L	L	UC	UC	UC	UC
Benjamin *et al*[14], 2005	121	Clinic, 17-35 yr, NA-PN	Tamil	8/9	CIS-R, ICD-10	94.1	90.2	UC	L	UC	UC	L	L	L
Werrett and Clifford[15], 2006	25	Clinic, 23-40 yr; 5-8 wk, 10-14 wk PN	Punjabi	12.5/13	CIDI, ICD-10	71.4	93.7	L	L	L	L	L	L	L
Fernandes *et al*[16], 2011	194	Clinic, 3rd trimester	Kannada	12/13	MINI-Plus, DSM-IV	100	84.9	UC	L	L	UC	L	L	L
Desai *et al*[17], 2011	200	Clinic, 18-35, up to 6 mo PN	Gujarati	10.5/11	SSI, DSM-IV	100	98	UC	L	UC	UC	L	L	L
Savarimuthu *et al*[18], 2012	137	Community 21-30 yr, 4-6 wk PN	Tamil	6/7	CI, ICD-10	85.3	77.7	UC	L	UC	L	L	L	L
Kalita *et al*[19], 2015	200	Clinic, 18-42 yr, 6 wk PN	Assamese	13	CI, ICD-10	88.9	85.3	UC	L	UC	H	L	L	L
Maity *et al*[20], 2015	105	Clinic, NA, NA	Bengali	13	NA	84	91	H	UC	H	H	H	H	H
Khapre *et al*[21], 2017	280	Community, 25 yr median, 2 wk PN	Marathi	12/13	SSI, ICD-10	93.8	94.9	UC	L	UC	UC	L	L	L

Patient selection (PS): Describe methods of patient selection; Index text (IT): Describe the index test and how it was conducted and interpreted; Reference standard (RS): Describe the reference standard and how it was conducted and interpreted; Flow and timing (F&T): Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2×2 table, and describe the interval and any interventions between index tests and the reference standard; H: High bias (if any signalling question was answered "no,"); L: Low bias (if the answers to all signalling questions for a domain were "yes,"); UC: Unclear (if insufficient data were reported to permit our judgment). PICO: Participants, Index measure, Comparative reference measure and Outcome of diagnostic accuracy; CIS-R: Clinical Interview Schedule (Revised); CI: Clinical Interview; CIDI: Composite international diagnostic interview; ICD-10: International Classification of Diseases, Edition 10; DSM-IV: Diagnostic and Statistical Manual, IVth Edition; MINIPlus: Mini International Neuropsychiatric Interview Plus; SSI: Semi-structured Interview; PN: Post-natal period; NA: Not available; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2.

namely the absence of a summary global diagnostic accuracy and clinical utility parameter for use in India for non-English EPDS. Hence we: (1) Establish the summary global diagnostic accuracy of the non-English EPDS versions in India; and (2) Evaluate the clinical utility of the measure for post-natal Depression.

MATERIALS AND METHODS

Literature search

Two researchers (SMC and ER) independently electronically searched for relevant published studies in the PubMed, EMBASE (international database), MEDKNOW and IndMED (regional database) databases as well as hand-searched to augment the search with cross-references, published conference abstracts, Government of India publications, and grey literature from January 2000 to February 2018. We combined the search terms as follows: "diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnostic"[All Fields]) AND accuracy[All Fields] AND ("psychiatric status rating scales"[MeSH Terms] OR ("psychiatric"[All Fields] AND "status"[All Fields] AND "rating"[All Fields] AND "scales"[All Fields]) OR "psychiatric status rating scales"[All Fields] OR ("Edinburgh"[All Fields] AND "postnatal"[All Fields] AND "depression"[All Fields] AND "scale"[All Fields]) OR "Edinburgh postnatal depression scale"[All Fields]) AND ("India"[MeSH Terms] OR "india"[All Fields].

Study selection and data extraction

Two other researchers (SR and SAV) extracted the required details independently, resolved any differences in extraction by consultation with another researcher (PSSR), and entered the information as electronic data. They extracted the participants, index measure, comparative reference measure and outcome of diagnostic accuracy details of each study. For a study to be included in the final analysis, it should have been conducted in India or among Indian populations, and must have compared the diagnostic accuracy of EPDS against either the Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) for PND as the reference standard. Finally, each study had to report sufficient data to construct 2 × 2 tables for calculating the true positive, false positive, false negative and true negative values of EPDS against the reference standard.

Quality appraisal and risk of bias

Two researchers (SAV and PMM) also appraised the quality of the studies with Quality Assessment of Diagnostic-Accuracy Studies, version 2 (QUADAS-2)[9]. We calculated the Deek's plot for publication bias[10].

Statistical analysis

We used the Area Under the Characteristic Curve of the Hierarchical Summary Receiver Operating Curve (HSAUROC), with random effects model, to establish the global diagnostic accuracy of EPDS[11]. This was the first outcome of this meta-analysis. Using the 2 × 2 table, we calculated the positive and negative likelihood ratios (+LR and –LR, respectively). From these likelihood ratios, we evaluated the post-test probabilities of EPDS using the Fagan's nomogram (Bayesian approach); these post-test probabilities indicating the clinical utility was the second outcome of our study[12]. We calculated the 95% confidence interval (95%CI) whenever indicated. All analyses were done at the study level and not at the participant level. The analyses were done with STATA (version 15) using the MIDAS and METANDI modules.

RESULTS

Study characteristics

The search strategies provided 2108 titles and the diagnostic accuracy of EPDS was documented in nine studies in seven of the official languages of India[13-21]. One study in Kannada was excluded, as it included participants during their third trimester of pregnancy and not the post-natal period[16]. Another study in Bengali was excluded due to the poor quality of the study[20]. Figure 1 captures the PRISMA details, and Table 1 summarises the participants, index measure, comparative reference measure and outcome of diagnostic accuracy details and QUADAS -2 appraisal of each of the studies that were included or excluded in the final analysis (n = 1227). The QUADAS-2 appraisal demonstrated that in the risk of bias criteria, one study was rated as "at low risk of bias" across all domains. A rating of an unclear risk of bias was the most common rating across the appraisal domains. The Deek's plot for publication bias is presented in Figure 2. In terms of applicability criteria, all seven studies were rated as applicable on all domains (Figure 3 for QUADAS-2 details). All studies had a cross-sectional design.

Diagnostic accuracy and clinical utility

The global diagnostic accuracy of EPDS as ascertained by HSAUROC was 0.97

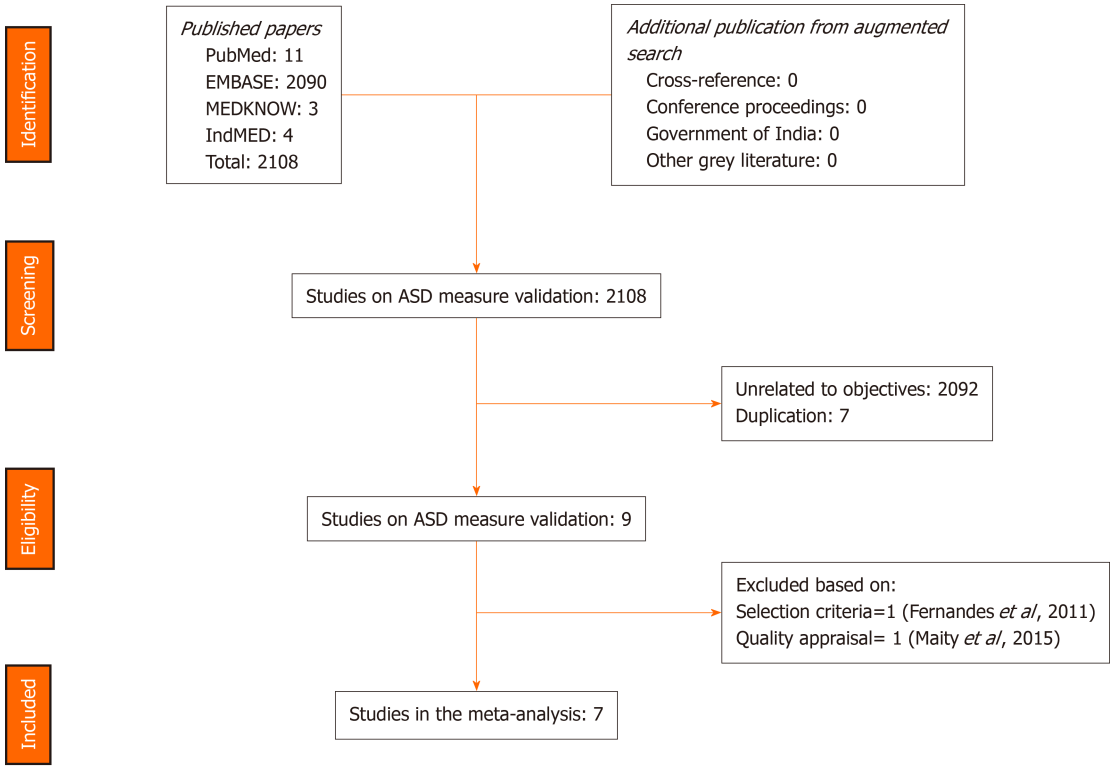


Figure 1 Overview of PRISMA selection process of studies.

(95%CI: 0.95-0.98) (Figure 4). The pre-test probability for the nomogram was 22%. For a +LR of 9, the positive post-test probability was 72% (95%CI: 68%, 76%) and for a -LR of 0.08, the negative post-test probability was 2% (95%CI: 1%, 3%) (Figure 5).

DISCUSSION

Firstly, the global diagnostic accuracy of EPDS was excellent for the five different non-English versions in India. This HSAUROC value of 0.97 when converted to a more comprehensible clinical effect size of Cohen's *d* or correlation coefficient *r* was 2.66 or 0.79, respectively[22]. This was a large effect size in the context of the diagnostic accuracy of EPDS when used as a screening measure for PND. Secondly, for the pre-test probability of 22%, the positive increment in diagnostic utility was 51% and the negative decrement was 20% for the post-test probability of EPDS. Given that the prevalence of PND in India is 22%[3], our incremental changes in post-test probability values have added considerable certainty to the diagnosis of PND when EPDS is used[12]. Thus, if a postnatal mother tests positive for EPDS, the chance she has PND increases from 22% to 72%; the clinician might therefore decide to actively engage in treatment. Conversely, if the patient tests negative, the chance of having PND decreases from 22% to 2%, and the clinician might decide not to actively treat the PND but engage instead in watchful waiting. Our finding about the diagnostic accuracy of EPDS versions is comparable with the values reviewed for the English versions in native English-speaking countries[6,7]. In comparison to some of the other selected non-English EPDS versions among African languages, the Chichewa version in Malawi, the Shona version in Zimbabwe, and the Nigerian version have relatively lower diagnostic accuracies than the summary value that is reported in this meta-analysis[23,24]. The translated version of EPDS in Afrikaans, Zulu, Tswana, Sotha, and Xhosa has demonstrated higher diagnostic accuracy for EPDS in South Africa[25]. Among European languages, the Danish version of EPDS has an Area Under the Curve of 0.96 and is comparable to our summary data[26], the Spanish version had an overall accuracy of 87.4%[27], and the French versions of EPDS has a sensitivity and specificity of 80% and 92%, and thus had lower diagnostic accuracy[28]. The other Asian language where EPDS has been validated includes Arabic[29], Chinese[30], and Japanese[31]; they have been found to have lower or similar diagnostic accuracies as in our meta-analysis.

The strengths of this study from a methodological perspective are that we followed

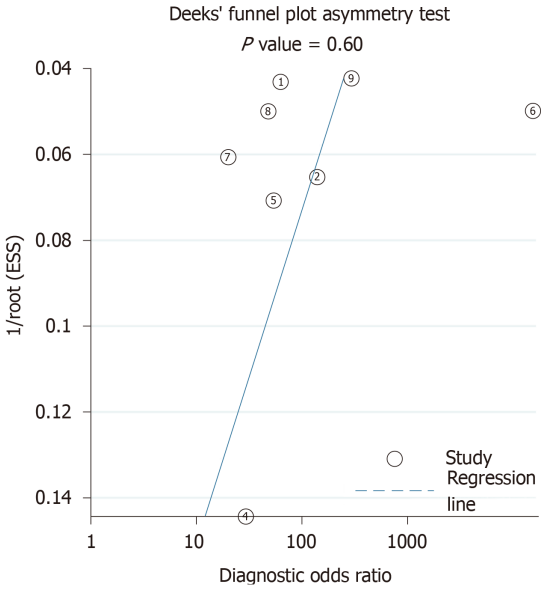


Figure 2 The Deek's plot for publication bias.

the guidelines recommended by the Cochrane Diagnostic Test Accuracy Protocol. To present the summary of the global diagnostic accuracy of the EPDS, we used a summary line (HSROC) then summary point, as studies with various EPDS threshold values and two reference standards were analysed together. Furthermore, we anticipated the sensitivity as well as specificity of EPDS to differ widely between studies from the literature, and used the random effects model over the fixed effects model for analysis[6,7]. There was no publication or small study bias in our meta-analysis. Finally, from the policy implication standpoint, in about 69069 births expected per day in India[32], the need to identify the 22% of mothers with PND and deliver the integrated management of mother-baby dyad is a huge task. However, this can be achieved if PND is identified and EPDS is used as a valuable measure[33]. The National Mental Health Program should routinely incorporate the use of EPDS as the screening measure for PND in India through its District Mental Health approach.

In light of these findings, we conclude that the EPDS, with its many language versions and its brevity, is eminently suited for the screening of PND in India, where mental health resources are low but burden is high.

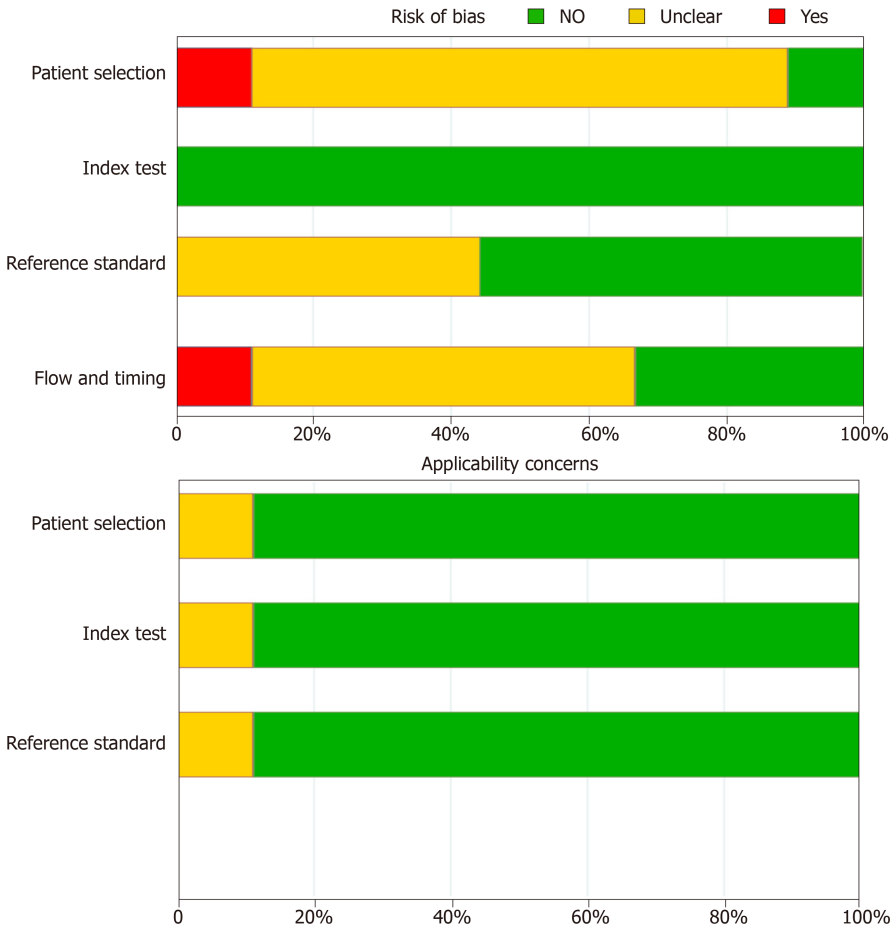


Figure 3 The average Quality Assessment of Diagnostic-Accuracy Studies, version 2 appraisal for all included studies.

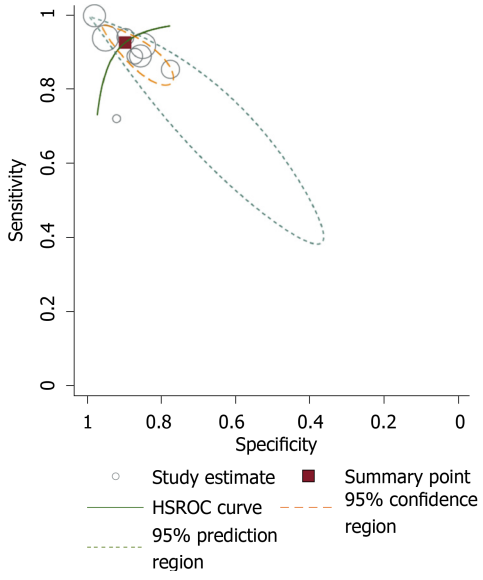


Figure 4 The Hierarchical Summary Receiver Operating Characteristic Curve of Edinburgh Postnatal Depression Scale with its confidence and prediction contours. HSROC: Hierarchical Summary Receiver Operating Curve.

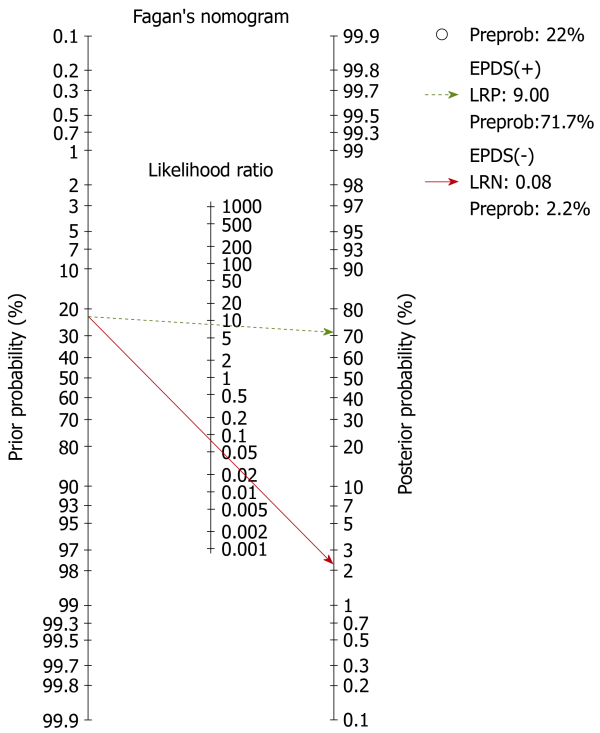


Figure 5 The post-test probability of Edinburgh Postnatal Depression Scale calculated with Fagan's nomogram.

ARTICLE HIGHLIGHTS

Research background

Various language versions of Edinburgh Postnatal Depression (EPDS) have been validated in India. The summary global diagnostic accuracy and clinical utility of these versions was established.

Research motivation

The diagnosis of postnatal depression (PND) is often missed or misdiagnosed. This affects both the mother and the baby, with significant morbidity. The widely used EPDS in India has to be proven for the early identification of PND.

Research objectives

The aim of this meta-analysis was to document the summary diagnostic accuracy and clinical utility of the various language versions of EPDS in India.

Research methods

Seven studies were included in the analysis following the PRISMA guidelines. We used Area Under the Characteristic Curve of the Hierarchical Summary Receiver Operating Curve, with random effect model, to summarize the diagnostic accuracy of EPDS; Fagan's nomogram was used for calculating clinical utility.

Research results

The global diagnostic accuracy of EPDS, as ascertained by Area Under the Characteristic Curve of the Hierarchical Summary Receiver Operating Curve, was 0.97 (95%CI: 0.95-0.98). For a PND prevalence of 22%, the positive post-test probability was 72% (95%CI: 68%, 76%) and the negative post-test probability was 2% (95%CI: 1%, 3%).

Research conclusions

We established the summary global diagnostic accuracy and clinical utility of the various versions of EPDS. The EPDS is effective in the early identification of PND.

Research perspectives

The EPDS in its various versions in India could be used for the scaling-up of PND treatment. The specific diagnostic parameters need to be further studied.

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MINIREVIEWS

Neuroendocrine, epigenetic, and intergenerational effects of general anesthetics

Anatoly E Martynyuk, Ling-Sha Ju, Timothy E Morey, Jia-Qiang Zhang

ORCID number: Anatoly E Martynyuk (0000-0002-9915-5584); Ling-Sha Ju (0000-0001-7266-0794); Timothy E Morey (0000-0003-2922-8984); Jia-Qiang Zhang (0000-0002-1367-9644).

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Anatoly E Martynyuk, Department of Anesthesiology and the McKnight Brain Institute, University of Florida College of Medicine, Gainesville, FL 32610, United States

Ling-Sha Ju, Timothy E Morey, Department of Anesthesiology, University of Florida College of Medicine, Gainesville, FL 32610, United States

Jia-Qiang Zhang, Department of Anesthesiology and Perioperative Medicine, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, Zhengzhou 450003, Henan Province, China

Corresponding author: Anatoly E Martynyuk, DSc, PhD, Professor, Department of Anesthesiology and the McKnight Brain Institute, University of Florida College of Medicine, 1600 SW Archer Road, PO Box 100254, Gainesville, FL 32610, United States.
amartynyuk@anest.ufl.edu

Abstract

The progress of modern medicine would be impossible without the use of general anesthetics (GAs). Despite advancements in refining anesthesia approaches, the effects of GAs are not fully reversible upon GA withdrawal. Neurocognitive deficiencies attributed to GA exposure may persist in neonates or endure for weeks to years in the elderly. Human studies on the mechanisms of the long-term adverse effects of GAs are needed to improve the safety of general anesthesia but they are hampered not only by ethical limitations specific to human research, but also by a lack of specific biological markers that can be used in human studies to safely and objectively study such effects. The latter can primarily be attributed to an insufficient understanding of the full range of the biological effects induced by GAs and the molecular mechanisms mediating such effects even in rodents, which are far more extensively studied than any other species. Our most recent experimental findings in rodents suggest that GAs may adversely affect many more people than is currently anticipated. Specifically, we have shown that anesthesia with the commonly used GA sevoflurane induces in exposed animals not only neuroendocrine abnormalities (somatic effects), but also epigenetic reprogramming of germ cells (germ cell effects). The latter may pass the neurobehavioral effects of parental sevoflurane exposure to the offspring, who may be affected even at levels of anesthesia that are not harmful to the exposed parents. The large number of patients who require general anesthesia, the even larger number of their future unexposed offspring whose health may be affected, and a growing number of neurodevelopmental disorders of unknown etiology underscore the translational importance of investigating the intergenerational effects of GAs. In this mini review, we discuss emerging

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experimental findings on neuroendocrine, epigenetic, and intergenerational effects of GAs.

Key words: Brain; General anesthetic; Sevoflurane; Corticosterone; Cortisol; Histone acetylation; Deoxyribonucleic acid methylation; Intergenerational effects; Gamma aminobutyric acid

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Core tip: The GABAergic general anesthetics may act as stressors and endocrine disruptors in neonates and young adults. They may induce two distinct types of long-term adverse effects: Neuroendocrine effects (the somatic effects) and epigenetic reprogramming of germ cells (the germ cell effects). The latter may pass neurobehavioral abnormalities to male offspring. Compared to the somatic cells, the germ cells may be more sensitive to the deleterious effects of general anesthetics, raising the possibility that the offspring may be affected even when levels of anesthesia are not harmful to the exposed parents. Further rigorous experimental testing of all these possibilities is required.

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INTRODUCTION

The number of surgeries performed globally has rapidly increased from 226.4 million in 2004 to 312.9 million in 2012, according to 2016 World Health Organization estimates[1]. Most of these surgeries and many non-surgical procedures require general anesthesia, which can be viewed as a state of pharmacologically induced "reversible brain coma"[2]. Despite complete reversibility of the primary effect of general anesthetics (GAs), *i.e.*, induction of the general anesthesia state, many studies in humans and almost all studies in laboratory animals provide evidence that GAs may leave persistent footprints of their brief presence in the body, *i.e.*, anesthetic exposure may lead to long-lasting functional abnormalities[3-7]. Investigations of anesthesia-induced abnormalities are currently restricted primarily to evaluating neurocognitive function in the exposed subjects[8-12], although it is biologically plausible that GAs may affect other functions/systems because their actions are not limited to neuronal effects involved in the mediation of a general anesthesia state. Still, as a result of these studies, the long-term adverse effects of GAs are an increasingly recognized health concern, especially in the very young and elderly[3-7]. The adverse effects of GAs during the perinatal period are of special concern[13-17] because mounting evidence indicates that at this stage of life the central nervous system and other body systems are highly susceptible to reprogramming by environmental factors/stressors[18-21]. Such environmental factors may include GAs, given the multiple molecular targets known to mediate their actions in the brain and throughout the body[22-25]. In support of this contention are reports of learning disabilities, long-term memory impairment, and attention-deficit hyperactivity disorders in patients who had anesthesia early in life[3,5,11,26,27]. Although several recent studies have not found negative neurocognitive consequences of relatively short (≤ 1 h) anesthesia exposures in children[6,7,28], both clinical and laboratory studies, including the most recent clinical assessments[29], agree that prolonged or repeated exposures to GAs that are frequently required for very sick children may result in significant neurocognitive abnormalities later in life[30]. Furthermore, a recent report of the effects on brain development of relatively short anesthesia exposure for cesarean delivery[31] further confirms that the current understanding of this phenomenon remains in an early stage.

Because of a widely accepted dogma that the brain is most susceptible to the deleterious effects of environmental stressors at the extreme of ages, investigations of the long-term adverse effects of GAs in young adults are scarce even in animal models. Several studies have assessed the effects of GAs in young adult rats,

primarily using rats of this age as comparisons to other age groups[4,32-34]. Aside from the fact that these studies found long-term effects of isoflurane in young adult rats, different isoflurane concentrations and exposure regimens make it difficult to compare the effects across these studies. Clearly, further research is needed to elucidate the full range of long-term effects of GAs in young adults. Importantly, the germ cells, which pass the genetic and epigenetic information from parents to offspring, can be susceptible to epigenetic reprogramming by environmental factors throughout the lifespan[35-39].

Laboratory and clinical studies provide evidence that alcohol, stress, endocrine disruptors, obesity, and even physical exercise may affect embryonic development and the phenotype of the offspring[40-44]. GAs share many molecular mechanisms of action with alcohol[45-49] and may act as endocrine disruptors and environmental stressors in animal models and humans. The spectrum of molecular actions of GAs and susceptibility of germ cells to epigenetic reprogramming by environmental factors across the lifespan support the possibility that the offspring may be affected by parental exposure to GAs regardless of the parental age at the time of exposure to GAs. In this mini review, we discuss emerging experimental findings on the neuroendocrine, epigenetic, and intergenerational effects of GAs.

NEUROENDOCRINE, EPIGENETIC, AND SECOND-GENERATION EFFECTS OF GENERAL ANESTHETICS

Research studies on the epigenetic multigenerational effects of environmental factors, such as alcohol, stress, endocrine disruptors, and others, have changed our thinking about the susceptibility of somatic and germ cells to alterations by environmental factors and the persistence of such alterations not only across the lifespan, but also through generations[36-38,40,42]. The potential of GAs to induce similar epigenetic effects, including reprogramming of the germ cell epigenome, and by extension intergenerational effects is supported by the notion that GAs share many molecular mechanisms of action with alcohol and may act as endocrine disruptors and environmental stressors in animal models and humans[45-49].

Endocrine disruptors can broadly be defined as agents that interfere with the functioning of the endocrine system. In support of the neuroendocrine effects of GAs are reports of significant rises in cortisol levels in pediatric patients after surgery or after anesthesia without surgery in healthy children[50,51]. Also, measurements of salivary cortisol levels in response to different levels of sedation in healthy children found a more than threefold increase in cortisol values, with the highest cortisol levels during the recovery phase[52]. Adult patients who received isoflurane-based tracheal general anesthesia compared to those who received bupivacaine-based epidural anesthesia had more than two times higher plasma levels of cortisol at the end of surgery, which was also more than four times higher compared to baseline levels in the same patients[53]. For a recent comprehensive review on cortisol levels associated with anesthesia/surgery see[54]. Importantly, our findings in rodents support the notion that GABAergic anesthetics act *via* specific molecular mechanisms to induce stress-like responses, rather than that GA-caused increases in glucocorticoid levels are the result of the systemic stress response because of uncontrolled physiological parameters during anesthesia. Thus, in neonatal rats, the gamma aminobutyric acid (GABA) type A receptor ($GABA_AR$) antagonist bicuculline at a low dose (0.01 mg/kg) or aromatase inhibitor formestane, administered prior to anesthesia with sevoflurane, prevented the sevoflurane-increased corticosterone secretion without an obvious effect on the sedation depth induced by the anesthetic (unpublished observations).

The inhibitory control of the corticotropin-releasing hormone-secreting hypothalamic paraventricular neurons by $GABA_AR$-mediated signaling and the positive modulation of this signaling by neuroactive steroids is one of the fundamental mechanisms of downregulating the stress response[55,56]. Due to relatively high and low expressions of the Cl^- transporters Na^+-K^+-$2Cl^-$ (NKCC1) and K^+-$2Cl^-$ (KCC2), respectively, immature neurons have elevated intracellular concentrations of Cl^-, the main charge carriers through $GABA_AR$ channels[57-61], a major substrate for the otherwise inhibitory effects of GABAergic anesthetics[22-25]. Activation of $GABA_ARs$ in immature neurons causes Cl^- efflux, membrane depolarization, activation of the voltage-gated Ca^{++} channels, and relief of the Mg^{++}-block of Ca^{++} permeable N-methyl-D-aspartate receptors[58-62]. The GABA-initiated Ca^{++} influxes regulate a wide spectrum of developmental processes from gene expression to synapse formation[61,62]. During the second postnatal week, $GABA_AR$-mediated signaling in the brain undergoes a fundamental transition from predominantly stimulating/excitatory to inhibitory, which is caused by a concomitant developmental downregulation of NKCC1 and,

most importantly, upregulation of neuronal-specific KCC2[61,62]. It is plausible that in the neonatal brain such $GABA_AR$ inhibitory signaling-mediated control of the stress response system is weakened or GABAergic anesthetics may even stimulate the stress response through positive modulation of depolarizing/excitatory $GABA_AR$ signaling at this age.

Consistent with stressor-like effects of GABAergic anesthetics, we found that a single exposure of neonatal rats to the GABAergic GAs sevoflurane or propofol was sufficient to cause multifold increases in corticosterone secretion and electroencephalography-detectable seizures at the time of anesthesia[63-67]. The anesthetic-caused increases in excitatory $GABA_AR$ signaling and corticosterone levels may be required for neonatal GABAergic anesthetic-induced seizures to occur[68,69]. Importantly, a single exposure to sevoflurane or propofol early in life induced neuroendocrine abnormalities[64,66,70-73] similar to those induced by repeated, but not single, maternal separations, a widely used rodent model of developmental effects of early-life stress in humans[74-78]. The GABAergic anesthetic-induced long-term neuroendocrine abnormalities, which were more robust in males, included increased anxiety-like behavior and exacerbated corticosterone responses to stress[64-67]. In addition, the rats, neonatally exposed to anesthesia, had elevated *Crh* mRNA levels in the hypothalamus, as well as up- and downregulated hypothalamic and hippocampal mRNA levels of *Nkcc1* and *Kcc2*, respectively[66,67,73]. Notably, delays in the $GABA_AR$ signaling transition to inhibitory have been linked in animal models and humans to a number of cognitive neuropsychiatric disorders, such as schizophrenia, autism spectrum disorder (ASD), and Rett syndrome[79-85]. For example, in Rett syndrome, a severe form of ASD, the methyl CpG binding protein 2 deficiency-induced KCC2 downregulation may play an important causal role[84,85].

When used at a low dose, bumetanide, a loop diuretic, is the most selective of the available inhibitors of NKCC1 activity[86,87]. Our lab and others have demonstrated that pretreatment of neonatal rats with bumetanide prior to anesthetic exposure ameliorated many of the acute and lasting developmental effects of GABAergic anesthetics, including: (1) Seizures; (2) Downregulated *Kcc2* levels; (3) Elevated levels of *Crh* mRNA; (4) Exacerbated corticosterone responses to acute stress; and (5) Behavioral abnormalities[63-66,88]. Bumetanide's ameliorating effects suggest that anesthetic-exacerbated $GABA_AR$-mediated stimulation/excitation in the neonatal rodent brain is an initial step in anesthetic-induced developmental abnormalities. Importantly, bumetanide exhibits promising therapeutic effects against ASD, schizophrenia, and Fragile X syndrome in animal models and humans[89-93], suggesting that these diseases and the GABAergic anesthetic-induced abnormalities may share similar mediating mechanisms. Our current understanding of rodent and human ontogeny supports the possibility that similar GA-sensitive mechanisms operate in rodents and humans early in life. Based on the intensity of synaptogenesis, a 1-wk-old rat can be compared to a 2- to 3-year-old human[94-98]. In animals, neonatal anesthetic exposure[63,65,72,99,100] and early-life stress[101-103] have profound long-term effects on synaptic morphology and function, suggesting that humans are vulnerable well into the postnatal period. Similar to the rodent brain during the first 2 postnatal weeks, the human brain is more excitable during the first year of life than at any other time, with seizures occurring in 3.5 per 1000 live births[104-106]. Human neonatal seizures are resistant to GABAergic antiepileptic drugs (AEDs) because of depolarizing/excitatory $GABA_AR$ signaling at this age[107,108]. Many human neonatal seizures can be detected only through electroencephalographies because they are not accompanied by clinical signs such as convulsions[109], which helps explain why epileptic seizures are not routinely reported in anesthetized human infants. In neonatal seizures with clinical manifestations, $GABA_AR$-enhancing AEDs depress convulsions but may exacerbate electrographic cortical seizure activity (electroclinical uncoupling)[110]. The NKCC1 inhibitor bumetanide, administered alone or in combination with GABAergic AEDs, may alleviate neonatal seizures in rodents and humans[111,112]. In humans, the KCC2 protein levels at birth are only about 20% of adult levels and significantly increase during the first postnatal year[86]. This late KCC2 increase during brain development may make KCC2 a highly susceptible molecular target for modulation by environmental factors, including GAs.

The heightened corticosterone responses to acute stress months after exposure to the GABAergic anesthetics early in life suggest that stressors in post-anesthesia life can further exacerbate developmental abnormalities, initially programmed by GABAergic anesthetics. This concept is supported by our findings that adult rats exposed neonatally for a relatively short time to anesthesia with etomidate or sevoflurane followed by a subsequent single episode of maternal separation exhibited developmental abnormalities significantly greater than those exposed to only one of the two interventions[66,73,113]. In further support of the idea that the long-term adverse outcomes of early-life anesthesia may result from a combination of the effects of GAs

at the time of anesthesia and the effects of "post-anesthesia" environmental factors, several laboratories have demonstrated that the adverse developmental effects of neonatal anesthesia in rodents may be alleviated, not only by pharmacological interventions before exposure to anesthesia, but also by post-weaning housing of the exposed animals in an enriched environment[114-116]. Environmental factors may alleviate or exacerbate the effects of neonatal anesthesia. In other words, two subjects exposed to the same anesthesia regimen may have different long-term outcomes based on post-anesthesia life experiences. In support of this possibility, Zhang *et al*[117] reported that rats neonatally exposed to sevoflurane and then housed from the time of weaning in isolation in enrichment-deprived environments exhibited reduced levels of brain-derived neurotrophic factor (BDNF), synaptic protein markers, and survival of new granule cells in the hippocampus, as well as behavioral abnormalities. On the other hand, rats that were exposed to the same regimen of anesthesia with sevoflurane and housed in groups in enriched environments had the same outcomes as their counterparts who were not exposed to sevoflurane. These findings further support the possibility that GABAergic anesthetics administered during early life can be considered environmental stressors that predispose the exposed subjects to stress vulnerability later in life. Identifying environmental factors that predispose humans to abnormal stress reactivity later in life and the mechanisms underlying their effects is of important clinical and basic neuroscience concern because dysregulated stress response systems have been linked to the pathophysiology of several neuropsychiatric disorders[118].

Environmental enrichment, which may alleviate the neurodevelopmental effects of early-life exposure to GAs in rodents, is not an issue for the majority of human patients because this is typical for most children. If similar mechanisms operate in humans, then brain development in healthy human patients who experience normal stress levels may be minimally affected, if at all, after exposure to general anesthesia early in life. However, most children who require general anesthesia during the early postnatal period inevitably experience a variety of stressors during life post-anesthesia exposure (*e.g*., diseases, pain, hunger, psychological stress). Such patients may be at risk of developing early-life, anesthetic-programmed neuroendocrine and neurocognitive abnormalities. The exacerbating effects of environmental stressors on long-term adverse outcomes of early-life exposure to GAs may be why several recent studies have not found negative neurocognitive consequences of relatively short (≤ 1 h) anesthesia exposures in healthy children[6,7,28], while studies in very sick children have[29]. It will be important to take this factor into consideration when planning new clinical studies. Further investigation of the interaction of adverse effects of early-life exposure to GAs and post-anesthesia stressors is important because it may identify not only the most vulnerable patients, but also those who are at diminished risk and would not benefit from delaying needed anesthesia-required interventions.

Histone acetylation and DNA methylation are important epigenetic mechanisms whereby environmental factors, in particular stress, affect brain development and function[119-121]. Histone acetylation facilitates gene transcription by enabling chromatin relaxation, while histone deacetylation results in stronger histone interaction with DNA, more compact chromatin structure, and repression of gene transcription. Histone acetylation is regulated by adding and removing acetyl groups to the N-terminal of histone tails by acetyltransferases and histone deacetylases, respectively[122-126]. Jia *et al*[99] found that repeated exposure of neonatal rats to sevoflurane led to increased levels of histone deacetylases 3 and 8 and reduced levels of acetylated histones H3 and H4 in the hippocampus. The sevoflurane-exposed rats had lower hippocampal density of dendritic spines and synaptic protein markers and exhibited impaired hippocampus function-based behavior. These effects of sevoflurane were alleviated by treatments with the histone deacetylase inhibitor sodium butyrate, suggesting a potential role of histone acetylation as one of the mediators of the developmental effects of GAs. The role of histone acetylation in GA-induced abnormalities in neonatal rodents has also been reported by other laboratories[127,128]. Furthermore, histone acetylation may be involved in the mediation of learning and memory dysfunction in offspring after pregnant rats exposed to sevoflurane, isoflurane, or propofol[129-131].

Ju *et al*[100] have found that repeated exposure of neonatal rats to sevoflurane resulted in increased expression of hippocampal DNA methyltransferases 3A/B (DNMT3A/B), but not DNA methyltransferase 1 (DNMT1). These enzymes catalyze DNA methylation at the 5′ position of cytosine residues adjacent to guanines (CpG sites), typically leading to long-term transcriptional repression. The activity of DNMT1 is responsible for maintenance of the remaining 5mC marks during cell divisions because of DNMT1 selectivity to hemi-methylated DNA, while DNMT3A/B are *de novo* DNMTs, which are induced by internal and external (environmental) stimuli[132,133]. In addition to increased expression of DNMT3A/B, the rats neonatally

exposed to sevoflurane had downregulated methyl CpG binding protein 2, hypermethylated the *Bdnf* gene, downregulated BDNF levels, and exhibited behavioral deficiencies[100]. The ability of sevoflurane to induce these abnormalities was significantly diminished in rats that were pretreated with a non-selective DNMT inhibitor, 5-aza-2'-deoxycytidin, prior to sevoflurane exposure[100]. On the other hand, Wu *et al*[134] found that exposure of neonatal rats to isoflurane, another inhaled anesthetic that has positive modulation of $GABA_AR$ activity like sevoflurane, induced a significant increase in the expression of hippocampal DNMT1. More experimental studies are needed before we can draw conclusions on the specific epigenetic mechanisms involved in the mediation of the adverse effects of a given GA or a class of GAs.

It has been established in a wide range of species, including humans, that environmental factors, in particular stress, acting *via* epigenetic mechanisms may affect not only the exposed subjects, but also future generations[135-139]. In contrast to studies of famine or war survivors, in which large groups of people in relatively compact living areas within a specific time period were affected[135,137,140], it is not trivial to link someone's neurodevelopmental abnormalities to his/her parent's relatively short exposure to GAs. Still, the emerging laboratory and clinical data demonstrate that the adverse effects of GAs may include epigenetic modifications, not only in the somatic cells of the exposed subjects, but also in their germ cell epigenome. Of most direct support of the possibility of epigenetic germ cell effects of general anesthesia in humans, Donkin *et al*[141] found that the DNA methylation status of 1509 genes in the sperm of male patients was changed 1 wk after bariatric surgery. The findings of epigenetic changes in spermatozoa just 1 wk after anesthesia/surgery suggest that the anesthesia/surgery may be an important cause of such changes and that even the mature human sperm is susceptible to epigenetic reprogramming by environmental factors. The latter is supported by the presence of DNMTs in mature human sperm[142]. Importantly, of the 1509 genes altered at 1 wk after the anesthesia/surgery, 1004 genes remained altered 1 year later[141]. Alarmingly, several small pilot clinical assessments found that anesthesia care providers may have altered female/male offspring ratios, also suggesting that persistent exposure to traces of the escaped GAs from scavenging in operating rooms might affect germ cells, and, hence, the next generation(s)[143-147].

To test whether neonatal exposure to anesthesia with sevoflurane can affect not only the exposed animals, but also their future offspring, we exposed male and female postnatal day (P) 5 rats (generation F0) to 6 h anesthesia with 2.1% sevoflurane[67]. On P90, the exposed and control rats were used as breeders to produce the second generation of rats (generation F1). We have found that adult offspring of parents who were neonatally exposed to sevoflurane exhibited neurobehavioral abnormalities. Irrespective of whether sires, dams, or both parents were exposed to neonatal sevoflurane, only F1 males, but not F1 females, were affected. F1 males exhibited reduced *Kcc2* Cl^- exporter expression and behavioral abnormalities. Bisulfate sequencing revealed CpG dinucleotide hypermethylation in the *Kcc2* promoter in the F0 sperm and ovary and in the hypothalamus and hippocampus of F1 males[67]. The correlation of impaired hippocampal *Kcc2* expression and hippocampus-dependent behavior in F1 males points to the involvement of epigenetic *Kcc2* modulation in the mediation of the intergenerational effects of sevoflurane[67]. Because DNA methylation is often associated with transcriptional repression, these data suggest that methylation of the *Kcc2* promoter in F0 gametes may contribute to sevoflurane-induced intergenerational impairment in *Kcc2* expression. The role of DNA methylation in the intergenerational effects of neonatal sevoflurane exposure in rats was also reported by Chastain-Potts *et al*[148]. Surprisingly, despite similar, but not identical, neurobehavioral abnormalities in the exposed parents and their male offspring, including downregulation of the *Kcc2* expression, the male offspring, in contrast to their exposed parents, exhibited corticosterone responses to stress that were the same as the corticosterone responses to stress in the male offspring of control parents[67]. These findings, taken together with the effects of GABAergic anesthetics in the exposed animals, suggest that GA-induced modulation of $GABA_AR$ signaling through reduced expression of *Kcc2* may be required but not sufficient to induce exacerbated responses to stress in adulthood.

Importantly, stress-like effects of GABAergic anesthetics may not be limited to the early postnatal period. Thus, exposure of young adult rats to sevoflurane on 3 alternating days starting on P56 resulted in similar increases in serum levels of corticosterone in male and female rats 1 h after the last exposure to the anesthetic[149]. However, long term, the exposed female rats were the same as the controls; they were not affected. On the other hand, contrary to the currently generally accepted view and our initial hypothesis that adult rats are resilient to the long-term adverse effects of GAs, the exposed young adult male rats developed neuroendocrine and behavioral

abnormalities. More than 3 months after exposure to sevoflurane, they exhibited not only an exacerbated hypothalamic pituitary adrenal axis response to stress, but their serum levels of luteinizing and testosterone hormones were also significantly increased, as was their expression of the hypothalamic gonadotropin-releasing hormone gene. The hypothalamic pituitary testicular axis functioning in the exposed adult male rats was also altered at the level of expressions of the hypothalamic aromatase and estrogen receptor α and β genes. The expressions of the aromatase and estrogen receptor α genes were significantly increased, while the expression of the estrogen receptor β gene was slightly, but significantly, decreased[149]. These findings demonstrate that anesthesia with sevoflurane alters (disrupts) not only the functioning of the hypothalamic pituitary adrenal axis, but also the hypothalamic pituitary testicular axis functioning[53]. We have previously demonstrated the role of estradiol in the acute adverse effects of sevoflurane in neonatal rats[69].

Similar to the effects of neonatal exposure to sevoflurane, sevoflurane administered to young adult male rats induced significant impairment in expressions of the hypothalamic and hippocampal *Kcc2* genes. Similar to adult rats that were neonatally exposed to sevoflurane, male and female rats exposed to sevoflurane in young adulthood had hypermethylated *Kcc2* gene in spermatozoa and ovarian tissue, respectively[149]. Interestingly, we have analyzed the same CpG sites in the *Kcc2* promoter region in the germ cells of rats that were exposed to sevoflurane neonatally or in young adulthood and found similar changes in their methylation regardless of the age of sevoflurane exposure[67,149]. These findings suggest that sevoflurane may induce germ cell effects *via* similar mediating mechanisms when administered to rats over a wide range of ages, from neonates to young adults. The similarities between the effects of neonatal and young adult exposure to sevoflurane were also evident in the offspring of the exposed parents. Thus, the *Kcc2* gene was hypermethylated and exhibited reduced expression in the hypothalamus and hippocampus of the F1 male, but not female, offspring of the exposed parents. These changes in the *Kcc2* gene in the hypothalamus and hippocampus of adult F1 male offspring were accompanied by behavioral deficiencies in the elevated plus maze and prepulse inhibition (PPI) of acoustic startle response tests, but their corticosterone responses to stress were not different from the controls[67,149]. The sevoflurane-exposed young adult male and female rats had similar acute increases in serum corticosterone levels and changes in DNA methylation status of the *Kcc2* gene in spermatozoa and ovarian tissue and passed neurobehavioral abnormalities to their male offspring, despite the finding that the exposed dams lacked the somatic effects[149]. These findings allow us to hypothesize that sevoflurane-induced corticosterone secretion at the time of anesthesia is involved in the anesthetic-induced germ cell effects and by extension the intergenerational effects. Also, the findings that the exposed but long-term physiologically unaffected dams, similar to the exposed and affected sires, pass deleterious effects of sevoflurane to their unexposed male offspring suggest that compared to the somatic cells, the germ cells are more sensitive to the deleterious effects of sevoflurane. This raises the possibility that male offspring may be affected even when the anesthesia level/duration is insufficient to induce significant abnormalities in their exposed parents. Future studies will be needed to test these hypotheses that may have important translational applicability.

We have tested the role of the neuron-specific *Kcc2* gene as a mediator of the germ cell and intergenerational effects of sevoflurane only because we have extensive background data supporting its involvement in the mediation of the somatic effects of neonatal and young adult exposure to sevoflurane in the exposed animals[64-67,149]. The findings that the *Kcc2* gene was affected in the parental somatic (brain) cells and germ cells, two effects that may not necessarily have similar mediating mechanisms, was surprising, on the one hand, but on the other hand suggested that the *Kcc2* gene could be one of many genes involved in passing on the intergenerational effects of the anesthetic. Indeed, using genome-wide reduced representation bisulfite sequencing, we found more than 2000 differentially methylated DNA regions in the sperm of adult rats neonatally exposed to sevoflurane compared to unexposed controls (unpublished observations). Future detailed investigation of various genes that are involved in the mediation of the intergenerational effects of sevoflurane and other GAs may help to identify a full spectrum of the biological intergenerational effects of GAs and may lead to new, unexpected parental GA-induced phenotypes in offspring. It is likely that the intergenerational effects of exposure to GAs in young adulthood are not limited to sevoflurane, as Tang *et al*[150] have shown behavioral abnormalities in the offspring of mice that were exposed to enflurane at 11 wk of age.

The weakness of most rodent behavioral paradigms is that they are difficult to directly replicate in humans. The results of our studies demonstrate that the PPI of startle was impaired in F0 rats exposed to sevoflurane as neonates or in young adulthood, as well as in their F1 male offspring[64-67,149]. Also, male and female rats,

exposed to sevoflurane neonatally, and male rats exposed to sevoflurane in young adulthood, exhibited heightened corticosterone responses to stress long term[64-67,149]. In humans, PPI can be measured safely *via* changes in the eyeblink reflex using nearly identical parameters as in rodents[151-155], while heightened stress-related cortisol levels can be readily measured in saliva[156,157]. If GAs induce similar effects in humans, the PPI of startle and saliva levels of cortisol may be used as objective, translatable, and easily and safely measurable biological markers of the adverse effects of GAs in humans. Identification of such a biomarker(s) will facilitate investigation of the underlying mechanisms of the adverse effects of GAs in humans to guide development of safer anesthetic approaches. Of particular relevance, one of the effective, tested therapeutic agents to alleviate the developmental effects of GABAergic anesthetics in rodent models, the NKCC1 inhibitor bumetanide[63-66,88], is approved for the treatment of various pediatric conditions and exhibits promising therapeutic effects in human studies of neurodevelopmental disorders[89-93].

Considering relatively well-studied molecular targets for GA actions and emerging evidence of similarities between the adverse outcomes of exposure to GABAergic anesthetics and psychiatric disorders, understanding the molecular mechanisms of the adverse effects of GAs may help to elucidate the mechanistic basis and etiology of complex neurodevelopmental disorders.

CONCLUSION

The results of recent studies raise many intriguing questions related to the types of adverse effects of GABAergic GAs and their underlying mechanisms, the answers to which may have important translational applicability for establishing safer general anesthesia, in particular, and for better understanding of the nature of neuropsychiatric disorders, in general. They suggest that GABAergic GAs, in particular sevoflurane, may act as stressors and endocrine disruptors in neonates and young adults. These stress-like effects of GABAergic GAs may be involved in the mediation of two distinct types of long-term adverse effects of GAs in the exposed rodents: neuroendocrine effects (the somatic effects) and epigenetic reprogramming of their germ cells (the germ cell effects). The latter may pass neurobehavioral abnormalities to male offspring. The intergenerational effects of sevoflurane are similar, but not identical, when administered to neonatal and young adult rats, suggesting that similar mediating mechanisms are involved over a wide range of ages at the time of anesthesia. The initial data suggest that compared to the somatic cells, the germ cells are more sensitive to the deleterious effects of sevoflurane, raising the possibility that the offspring may be affected even when levels of anesthesia are not harmful to the exposed parents. The long-term adverse effects of GAs in the exposed young adult male rats suggest that current views on the window of vulnerability to the adverse effects of GAs in rodents (up to the first 2 postnatal weeks)[158,159], and, hence, the United States Food and Drug Administration recommendations to avoid GAs in children younger than 3[160], may need to be reconsidered to include more advanced ages. All of these possibilities may have important translational applicability if confirmed; further rigorous experimental testing is required.

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MINIREVIEWS

Abdominal pain related to adulterated opium: An emerging issue in drug addicts

Maryam Vahabzadeh, Bruno Mégarbane

ORCID number: Maryam Vahabzadeh (0000-0002-6234-1834); Bruno Mégarbane (0000-0002-2522-2764).

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Maryam Vahabzadeh, Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Bruno Mégarbane, Department of Medical and Toxicological Critical Care, Lariboisière Hospital, Paris-Diderot University, INSERM UMRS-1144, Paris 75010, France

Corresponding author: Bruno Mégarbane, MD, PhD, Professor, Department of Medical and Toxicological Critical Care, Lariboisière Hospital, Paris-Diderot University, INSERM UMRS-1144, 2 Rue Ambroise Paré, Paris 75010, France. bruno.megarbane@lrb.aphp.fr

Abstract

Lead may contaminate opium, heroin and illicit opiates and is particularly observed in Iran. Lead, a natural heavy metal is able to interfere with several organ functions after ingestion or inhalation. Lead poisoning manifestations are non-specific and thus lead poisoning remains difficult to diagnose. Among the manifestations, abdominal pain is almost the most frequent symptom causing patients to seek medical care. In patients with a history of opium addiction presenting with moderate-to-severe abdominal pain, lack of diagnosis of lead toxicity may thus result in time-consuming and unnecessary medical work-ups that can end up in invasive surgery. This paper aims to briefly review abdominal pain as an emergency issue and the leading symptom of lead poisoning that brings most of the patients to healthcare facilities. All published adult cases and case series of opium addicts admitted with abdominal pain due to lead-adulterated opium consumption have been reviewed. A trend of increasing numbers of lead poisoning cases has recently emerged among opium addicts in Iran. Due to the non-specific manifestations and hazardous effects, psychiatrists and emergency physicians should consider lead poisoning in patients with a past or present history of opium addiction referred for acute abdominal pain, particularly in case of colicky abdominal pain.

Key words: Addiction; Opium; Lead; Poisoning; Abdominal pain; Toxicity

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Core tip: Lead may contaminate opium, heroin and illicit opiates, as is particularly observed in Iran. Abdominal pain is almost the most frequent symptom bringing the patients to medical care. Psychiatrists and emergency physicians should be aware of this complication and consider lead poisoning in opiate users referred for acute abdominal pain. Specific early management is crucial to improve prognosis.

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INTRODUCTION

Toxicity from heavy metals can occur following their overload in the body due to exposure to various sources. Considered as one of the highly toxic heavy metals, lead is naturally available in metallic and organic forms and can interfere with the function of several organs such as the central nervous system, the liver, the kidneys, the hematopoietic and cardiovascular systems[1]. Different sources of exposure are responsible for lead toxicity in humans, mainly drinking water, paint, occupational exposure and leaded gasoline[2]. Metallic lead can enter the body *via* ingestion (depending on the age and nutritional status) and inhalation (depending on the particle size)[3]. However, the majority of lead poisonings are due to ingestion and its consequent absorption occurs in the smaller intestine resulting in its accumulation in blood, bone, and fatty tissues[4].

Also known as plumbism, lead poisoning is still one of the main areas of concern in the developing world including Iran. Even though cases due to occupational lead poisoning have declined, overall metallic lead poisoning has markedly increased over the past few years[5].

Lead poisoning is difficult to diagnose due to non-specific manifestations. The main symptoms and signs include moderate-to-severe abdominal pain (also known as lead colic), appetite loss, constipation, anemia, liver and renal function impairment, and neurologic complications. Major risk factors for lead toxicity are young age (children), lack of minerals and protein in the diet, as well as poor socioeconomic conditions[4]. However, another notable major and recently recognized risk factor for lead poisoning is addiction to opium.

Lead poisoning due to abuse of contaminated opium was first reported in 1970s[6,7] and subsequently in 1989 following lead-contaminated heroin[8]. Interestingly, lead poisoning has been reported from lead-contaminated opium available in the Iranian market[9] while opium samples were confirmed to be contaminated with lead in Kerman province of Iran[10]. Failure to detect or misdiagnosis of lead poisoning in patients with a history of opium addiction presenting with abdominal pain may result in time-consuming gastrointestinal work-ups or even unnecessary abdominal surgery[11]. The current paper aims to review abdominal pain as the leading emergent symptom of lead poisoning referring opiate addicts to healthcare facilities. To address this goal, we reviewed all published cases and series of adult drug addicts presenting with abdominal pain attributed to lead poisoning from lead-adulterated opium.

LEAD TOXICITY

Chemical properties of lead

Lead is a bluish-gray silvery metal with atomic number of 82 and two isotopes ^{206}Pb and ^{208}Pb, and is available in two forms of metallic (also called inorganic) and organic lead (tetraethyl and tetramethyl lead). Lead has no particular taste or smell, and at atmospheric pressure, melts at 621.3 °F (327.4 °C), and boils at 1740 °C[12].

Exposure to lead

Exposure to lead may result in multisystemic toxicity. The risk of exposure to lead is higher among children and those with certain occupations. However, lead exposure in the workplace alone does not count as significant source of poisoning[13].

Upon exposure, lead is mainly absorbed from the gastrointestinal and respiratory systems. Over days to years, it accumulates in the body, particularly in bones, before manifestations occur. Also known as plumbism, lead poisoning is defined as abnormally elevated concentrations of lead in the blood resulting in non-specific symptoms and signs. Depending on the severity of poisoning, it can cause gastrointestinal manifestations such as abdominal pain and constipation, in addition to anemia, impairment of the nervous system, liver, kidney, heart, and reproductive system as well as developmental impairment in children. The exact mechanism by which lead exerts its toxic effects on the GI is not yet known. However, some

theoretical mechanisms are change in luminal ion transport, impairing intestinal motility, and spasmodic contractions in smooth muscles of the intestinal wall. The latter is considered to be one of the major causes of abdominal pain in lead-poisoned patients. The limit of concern for blood lead level (BLL) in children is 5 μg/dL, while it is much higher for adults (above 25 μg/dL)[14].

Over the past decade, one concerning source of exposure to lead was reported to be lead adulterated opium in Iran, although identified last century[6,7]. Iran lies in the major pathway of opium trafficking in the Middle East. According to the United Nations Office on Drug and Crime, 74% of the world opium seizures and 25% of the world heroin and morphine seizures in 2012 occurred in Iran[15]. Therefore, opium addiction is one of the major governmental and health challenges in the country. Although not yet widely reported, lead-contaminated opium has caused increasing numbers of poisonings to be referred to emergency departments and clinical toxicology centers.

REVIEW OF LEAD POISONING REPORTS DUE TO ADULTERATED OPIUM

Masoodi *et al*[9] first reported three male patients from Iran with acute abdominal pain, abnormal liver function tests, and anemia due to chronic oral opium use. None of the patients had occupational exposure and their chief complaint was abdominal pain and varying degrees of constipation. All patients were withdrawn from opium while two with BLLs above 80 μg/dL received chelating agent ($CaNa_2EDTA$). All were asymptomatic with normal laboratory tests after 3-4 wk of follow-up.

Further reported cases of lead poisoning due to lead-contaminated opium are depicted in Table 1, with the country of patient origin and additional clinical and laboratory data.

As shown in Table 1, the majority of cases of lead poisoning due to lead-contaminated opium[9,11,16-28] are surprisingly reported from Iran with the dominance of men. The case reports from The Netherlands[17,27] and the United Kingdom[23] also concerned two Iranians, one immigrant abusing opium from Iranian suppliers and one Persian citizen addicted to inhalational opium, respectively.

According to Table 1, the main features of lead poisoning are portrayed as gastrointestinal, hepatic and hematologic disorders. Manifestations in opium abusers were clearly attributable to the elevated BLL in comparison with non-addicts; hence, determination of BLL in suspected cases can definitively confirm the diagnosis[29]. Although abdominal pain is usually seen with BLL above 80 μg/dL, these reports are good evidence for the assumption that occurrence of abdominal pain, is not related to BLL[25]. On the other hand, there was a significant correlation between BLL and duration of drug abuse in opium addict cases ($r = 0.398$, $P = 0.022$). The odds ratio of having BLL ≥ 100 μg/dL in oral opium users was 2.1 (95%CI: 0.92-4.61; $P = 0.43$)[30].

It is not exactly known how much lead is added to opium samples in the Iranian black market. However, chemical analysis of a sample by atomic absorption spectrometry, recognized as the method of choice, showed 35.2 mg of lead per 100 g of opium[19]. In another study from Iran, random samples from various sources were analyzed using atomic absorption spectrometry, and the mean concentration of lead in the samples was 1.88 ± 0.35 ppm[10]. Chia *et al*[7] reported the level of lead in contaminated opium samples to be 33.8 mg per 100 g of opium.

Chronic abuse of opium with such low levels of lead over months to years results in lead accumulation and consequently severe plumbism. This poisoning can be easily misdiagnosed as it mimics several other medical conditions such as surgical acute abdomen, withdrawal symptom, crisis of sickle cell anemia, cholecystitis, acute porphyria, and nephrolithiasis[20,31]. Therefore, lead poisoning should be considered in the differential diagnosis of patients with moderate to severe abdominal pain.

All symptomatic patients with high BLL should undergo treatment following medical consultation with a clinical toxicologist. The treatment plan essentially consists of oral opium cessation, probably with the help of rehab programs, in addition to the administration of chelating agents such as dimercaprol (BAL: British anti-lewisite), $CaNa_2EDTA$, succimer (DMSA: dimercapto-succinic acid), and more rarely D-penicillamine[2]. Decision on which chelator should be used depends on the BLL, clinical manifestations, and laboratory results[14].

Complications of lead poisoning are reversible, providing early diagnosis and appropriate treatments are made; however, neurotoxicity may be permanent following significantly elevated BLLs and delayed specific treatment[18]. Timely detection and proper therapies for lead poisoning in an opium-addicted individual with the chief complaint of abdominal pain cannot only obviate the need for

Table 1 Reports of lead poisonings due to adulterated-opium abuse and their supplementary data

Type of study	Country	Gender–age/ mean age (y/o)	Route of abuse	Major clinical findings	Laboratory findings	BLL (μg/dL)	Treatment	Ref.
Case report	Iran	M-34	Ingestion	AP, N/V	Anemia, basophilic stippling of erythrocytes, elevated liver enzymes	95	$CaNa_2EDTA$	[9]
Case report	Iran	M-57	Ingestion	AP, nausea, severe constipation	Anemia, elevated liver enzymes	81	$CaNa_2EDTA$	[9]
Case report	Iran	M-45	Ingestion	Epigastric and periumbilical AP	Anemia, elevated liver enzymes	37.5	Opium cessation	[9]
Case report	Iran	M-65	Ingestion	AP, Burton's line, generalized ileus, N/V	Anemia, elevated liver enzymes	150	Dimercaprol + $CaNa_2EDTA$	[11]
Case report	Iran	M-25	Ingestion and inhalation	AP, malaise, N/V, weakness, excess sweating, dark urine, generalized bone pain	Anemia, elevated liver enzymes	350	Dimercaprol + $CaNa_2EDTA$	[16]
Case report	Netherlands	M-40	Ingestion	AP	Anemia, basophilic stippling, elevated liver enzymes	86	Dimercaprol + $CaNa_2EDTA$	[17]
Case report	Iran	M-40	Ingestion	Paresthesia in upper and lower extremities, low muscle strength, abdominal tenderness, late onset quadriplegia	Anemia, elevated liver enzymes	> 200	Dimercaprol + $CaNa_2EDTA$, followed by Succimer	[18]
Case report	Iran	M-32	Ingestion	AP, constipation, loss of appetite	Basophilic stippling	50	Dimercaprol	[19]
Descriptive, cross-sectional	Iran	M/F-average age: 41.8 ± 13.5	Ingestion	AP, anorexia, weight loss, constipation, nausea	Anemia	Average: 145 ± 61	NA (referred to toxicologists)	[20]
Descriptive, retrospective	Iran	M-20 to 39	Inhalation	Abdominal cramps	Anemia	Average: 109 ± 37.6	Dimercaprol ± $CaNa_2EDTA$	[21]
Case report	Iran	M-38	Ingestion and inhalation	Severe AP, Burton's line, muscle weakness, myalgias, and bad temper	Basophilic stippling	73	Dimercaprol + $CaNa_2EDTA$, DP	[22]
Case report	Singapore	F-40	Ingestion and inhalation	Severe lower AP	Anemia, punctate basophilia	NA	Calcium gluconate, calcium disodium versenate	[7]
Case report	Singapore	M-63	Ingestion	AP	Anemia, punctate basophilia	NA	Calcium gluconate, calcium disodium versenate	[7]

Case report	United Kingdom	M-46	Inhalation	Colicky AP, constipation, irritability and malaise	Extravascular haemolytic anaemia with punctate basophilic stippling	113.8	CaNa2EDTA	[23]
Case report	Iran	M-32	Ingestion	Dysarthria and progressive upper limb weakness following a refractory AP, constipation, nausea and headache	Anemia, high liver function tests and bilirubin	256	DP	[24]
Case report	Iran	F-36	Ingestion	Sever colicky AP, NV, Pleuritic chest pain, ejection fraction 30%, massive bilateral pleural effusion	Anemia (hypochromic-microcytic)	78	CaNa2EDTA	[25]
Case series	Iran	M/F-average age: 50.4 ± 13.4	Ingestion	Acute sever AP	Anemia	Average: 76.2	NA	[26]
Case series	Netherlands	M-average age: 44	Ingestion	AP, NV	Anemia, elevated liver enzymes	Average: 179.4	CaNa2EDTA	[27]
Case series	Iran	M-average age: 49.82 ± 11.52	Ingestion	AP, Loss of Appetite, Sleep Disturbance, Fatigue, Constipation	Anemia	Average: 93.36 ± 27.84	DP	[28]

M: Male; F: Female; N/V: Nausea and/or vomiting; AP: Abdominal pain; BLL: Blood lead level; NA: Not available; DP: D-penicillamine.

unnecessary medical evaluations or procedures and decrease its perilous complications such as loss of consciousness and paralysis[32] but also reduce the financial burden on patients and healthcare systems.

CONCLUSION

Despite a decrease in the frequency of occupational lead poisoning, a new trend of lead poisoning has recently emerged among opium addicts, mainly in Iran. Because of non-specific manifestations and hazardous effects of lead poisoning, this critical poisoning should be considered in the medical approach to any patient with a history of opiate addiction presenting to the emergency department with acute abdominal pain and particularly colicky abdominal pain.

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ORIGINAL ARTICLE

Observational Study

Effects of age and sex on clinical high-risk for psychosis in the community

Frauke Schultze-Lutter, Benno G Schimmelmann, Rahel Flückiger, Chantal Michel

ORCID number: Frauke Schultze-Lutter (0000-0003-1956-9574); Benno G Schimmelmann (0000-0002-8980-1466); Rahel Flückiger (0000-0003-1228-7267); Chantal Michel (0000-0003-1165-6681).

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Frauke Schultze-Lutter, Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Düsseldorf 40692, Germany

Benno G Schimmelmann, Rahel Flückiger, Chantal Michel, University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bern 3000, Switzerland

Benno G Schimmelmann, University Hospital of Child and Adolescent Psychiatry, University Hospital Hamburg-Eppendorf, Hamburg 20246, Germany

Corresponding author: Frauke Schultze-Lutter, MSc, PhD, Assistant Professor, Head of Early Detection Research Unit, Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Bergische Landstraße 2, Düsseldorf 40629, Germany. frauke.schultze-lutter@lvr.de

Abstract

BACKGROUND

Recent reports of both heightened prevalence rates and limited clinical relevance of clinical high-risk (CHR) criteria and their relevant symptoms in children and adolescents indicate an important role of neurodevelopment in the early detection of psychoses. Furthermore, sex effects in CHR symptoms have been reported, though studies were inconclusive. As sex also impacts on neurodevelopment, we expected that sex might have an additional contribution to age in the prevalence and clinical relevance of CHR symptoms and criteria.

AIM

To investigate age and sex effects on CHR criteria and symptoms and their association with psychosocial impairment and mental disorder.

METHODS

In this cross-sectional cohort study, n = 2916 8- to 40-year-olds, randomly drawn from the population register of the Swiss canton Bern, were assessed in semi-structured interviews by phone or face-to-face for CHR symptoms and criteria using the Structured Interview for Psychosis-Risk Syndromes and the Schizophrenia Proneness Instrument in its child and youth, and adult version, respectively. Furthermore, social and occupational functioning and DSM-IV axis I disorders were assessed. Simple and interaction effects of age and sex on CHR symptoms and criteria, and interaction effects of age, sex, and CHR symptoms and criteria on presentation of functional impairment and of non-psychotic disorder were investigated using logistic regression analyses.

RESULTS

and is on the speakers board of Takeda (Shire) and Infectopharm.

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STROBE statement: The "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines were carefully observed throughout the preparation of this manuscript.

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Altogether, 542 (18.6%) participants reported any CHR symptom; of these, 261 (9.0%) participants reported any one of the 11 criteria relevant cognitive and perceptual basic symptoms, and 381 (13.1%) any one of the five attenuated or transient psychotic symptoms (attenuated psychotic symptoms/brief intermittent psychotic symptoms). Fewer participants met any one of the CHR criteria (n = 82, 2.8%) or any one of the three recently recommended CHR criteria (n = 38, 1.3%). Both age and sex were significantly ($P < 0.05$) associated with CHR symptoms and criteria, mostly by younger age and female sex. Though slightly differing between symptom groups, age thresholds were detected around the turn from adolescence to adulthood; they were highest for cognitive basic symptoms and CHR criteria. With the exception of the infrequent speech disorganization attenuated psychotic symptom, the interaction of age with CHR symptoms and criteria predicted functional impairment; whereas, independent of each other, sex and CHR symptoms mostly predicted mental disorders.

CONCLUSION
Age and sex differentially impact on CHR symptoms and criteria; these differences may support better understanding of causal pathways. Thus, future CHR studies should consider effects of sex and age.

Key words: Psychosis; Clinical high-risk; Attenuated psychotic symptoms; Basic symptoms; Community; Age; Sex; Interview assessment; Prevalence

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Core tip: Age and sex are crucial aspects in neurodevelopment and are partly interrelated, presenting as important factors in mental disorders related to neurodevelopment, such as psychosis. However, both age- and sex-related aspects are frequently neglected in the early detection of psychosis. Therefore, this highly original study examined the association of age and sex with the presentation and clinical relevance of clinical high-risk criteria and their constituting symptoms in a large community sample of 8- to 40-year-olds. Next to confirming the important role of age and sex, their differential relations to clinical high-risk symptoms reveal important insight in possible causal pathways.

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INTRODUCTION

Psychoses, especially schizophrenia-spectrum psychoses, are severe mental disorders that tend to take an unfavorable course, in particular when the first episode occurs before age 18[1,2], and for this reason, incur immense costs and are a main cause of disability[1] already in adolescents[3]. In adolescents, this is despite the fact that the majority of first episodes of psychoses have their onset in adulthood, mostly before age 24[4,5]. Furthermore, psychoses affect more men than women[6], in particular after childhood and adolescence, and before age of 45 to 50[5,7]. These age and sex effects on incidence rates, and their interaction, are considered to reflect the fundamentally neurodevelopmental nature of psychoses, whereby development involves two critical time windows – early (perinatal) brain development and adolescence – that together produce the symptomatic manifestations of the disorder[1].

Starting in the 1980s, it was increasingly demonstrated that the duration of untreated first-episode psychosis as well as of its prodrome of mostly several years duration is related to poorer outcome[8], especially in psychoses with an onset before age 18[2,9,10]. Thus, it was concluded that an earlier detection and treatment of psychoses – preferably before their first episode – was needed[11]. Subsequent studies on adult patients produced two complimentary approaches to detect psychosis early,

in its clinical high-risk (CHR) state[12,13]: The ultra-high risk (UHR) and the basic symptom (BS) approach, together consisting of five alternatively employed criteria (Table 1).

However, following the increasing involvement of younger age groups in the early detection of psychotic disorders, concerns were raised about the likely impact of age, *i.e.*, developmental aspects on the prevalence, clinical relevance, and psychosis-predictive value of CHR symptoms and criteria[17]. These concerns were corroborated by significantly lower conversion-to-psychosis rates in UHR samples comprising exclusively children and adolescents compared to adult or mixed adult-adolescent samples[13], and by predominately negative associations between age and CHR criteria and symptoms in both clinical[18-23] and community studies[24,25]. Interestingly, when age effects were studied in child and adolescent samples only[22], older adolescents showed better functioning and lower depressive scores; and fewer adolescents than adults reported BS criteria in addition to the main UHR criterion, *i.e.*, the attenuated psychotic symptoms (APS) syndrome (APSS)[21]. Details on studies of age effects on CHR symptoms and criteria is provided in the supplementary text 1. As regards effects of sex, despite reported sex differences in prevalence of psychoses and psychosis-spectrum disorders, and their symptom distributions[6,26-29], sex effects on the clinical significance and psychosis-predictive value of CHR symptoms and criteria have been less studied and, apart from more negative symptoms in males, are frequently conflicting[30-43]. Details on studies of sex effects on CHR symptoms and criteria is provided in the supplementary text 2.

Aims and hypotheses

It was speculated from findings on age thresholds in CHR symptoms in the community[24,25] that sex differences in brain and cognitive maturation[44-47] might lead to lower age thresholds in the clinical significance of BS and possibly APS in females compared to males. In addition, due to the lack of studies on both age and sex effects on CHR symptoms and criteria, we investigated the effect of both age and sex on the prevalence of CHR criteria and symptoms and on their association with psychosocial impairment and mental disorder in a large community sample of 8- to 40-year-olds.

MATERIALS AND METHODS

Recruitment and sample

The sample was composed of community participants in two studies: The "Bern Epidemiology At-Risk" (BEAR) study[48,49] and the "Binational Evaluation of At-Risk Symptoms in Children and Adolescents" (BEARS-Kid) study[24,25]. Both studies used a stratified sampling method to obtain a representative sample of 7370 people aged 16–40 years, in the BEAR study (response rate: 63.4%), and of 980 minors aged 8-17 years, in the BEARS-Kid study (response rate: 32.6%), from the predominantly Caucasian people registered in the semi-rural Canton of Bern (approximately 1 Mill.) and the city of Bern and its urban hinterland (approximately 200000), respectively. The city of Bern is the largest city of the Canton Bern and has approximately 134000 citizens. In the Canton Bern, 21% of the population are non-Swiss; 80% of these are from European countries. Potential participants were randomly drawn from the obligatory population register including their address, date of birth, sex, nationality, and parents' names (for minors). Telephone numbers were subsequently searched in directories and the Internet.

In both studies, first contact was established by an information letter on the aims of the respective study, voluntariness of participation, and anonymous use of data in group statistics. For the BEAR study, participation in the telephone interview was equated with provision of informed consent; for the BEARS-Kid study, written informed assent/consent was obtained from participants and their parents. Both studies had been approved by the ethics committee of the University of Bern (KEK-BE 172/09 and 174/10).

In both studies, eligibility criteria included main residence in Canton Bern, appropriate age, and an available telephone number. Interviews were discontinued if participants had a past or current diagnosis of psychosis or insufficient understanding of German, French, or English. Recruitment and telephone assessments for the BEAR study were conducted over 3.5 years; recruitment and face-to-face assessments for the BEARS-Kid study over 3.3 years. Prior to merging data, a feasibility study examining the correspondence of telephone and face-to-face assessments of CHR had found excellent concordance rates (78%-100%) between these two assessment modes[50]. This finding demonstrated that data of both studies could be merged and compared without danger of introducing a systematic assessment bias.

Table 1 Clinical high risk for psychosis criteria

Ultra-high risk (UHR) criteria as per the Structured Interview for Psychosis-Risk Syndromes (SIPS) and basic symptom (BS) criteria as per the Schizophrenia Proneness Instruments (SPI-A/SPI-CY)[15,16]
UHR: Brief Intermittent Psychotic Symptoms Syndrome (BIPSS)
≥ 1 of the following SIPS positive (P) items scored 6 = "severe and psychotic" with first appearance in the past 3 months and a presence of at least several minutes per day at a frequency of at least once per month but less than 7 d:
P1 Unusual Thought Content/Delusional Ideas
P2 Suspiciousness/Persecutory Ideas
P3 Grandiose Ideas
P4 Perceptual Abnormalities/Hallucinations
P5 Disorganized Communication
UHR: Attenuated Psychotic Symptoms Syndrome (APSS)
≥ 1 of the above P-items scored 3 = "moderate" to 5 = "severe but not psychotic" with a first appearance within the past year or current rating one or more scale points higher compared to 12 mo ago, and with an occurrence of an average frequency of at least once per week in the past month.
UHR: Genetic Risk and Deterioration Syndrome (GRDS)
Patient meets SIPS-criteria for Schizotypal Personality Disorder or has 1st-degree relative with a psychotic disorder, and has experienced > 30% drop in the global assessment of functioning score over the last month compared to 12 mo ago
BS: Cognitive-Perceptive Basic Symptoms (COPER)
≥ 1 of the following BS with a score of ≥ 3 = "frequency of at least several times in a month or weekly" within the last 3 mo and with first occurrence ≥ 12 mo ago:
Thought interference
Thought perseveration
Thought pressure
Thought blockages
Disturbance of receptive speech
Decreased ability to discriminate between ideas/perception, fantasy/memories
Unstable ideas of reference
Derealization
Visual perception disturbances (excl. hypersensitivity to light or blurred vision)
Acoustic perception disturbances (excl. hypersensitivity to sounds)
BS: Cognitive Disturbances (COGDIS)
≥ 2 of the following BS with a score of ≥ 3 within the last 3 mo:
Inability to divide attention
Thought interference
Thought pressure
Thought blockages
Disturbance of receptive speech
Disturbance of expressive speech
Unstable ideas of reference
Disturbances of abstract thinking
Captivation of attention by details of the visual field

According to the definitions of the American Association for Public Opinion Research[51], the contact rates of those eligible were 94.8% in the BEAR study, and 82.7% in the BEARS-Kid study; refusal rates were 30.2% and 49.2%. Main reasons for refusal were lack of interest in the topic or lack of time; these reasons were named in both studies by roughly every second and every third refuser, respectively.

Altogether 2683 persons between the ages 16-40 years (inclusive) participated in the BEAR study, 233 persons aged 8-17 years (inclusive) in the BEARS-Kid study. Thus, our final sample (n = 2916) included 2539 (87.1%) adults and 377 (12.9%) children/adolescents. As in earlier studies[27,28,45,49], these were divided into seven age groups for the examination of simple age effects: 8-12 years (n = 117), 13-15 years (n = 69), 16-17 years (n = 191), 18-19 years (n = 167), 20-24 years (n = 493), 25-29 years (n = 319), and 30-40 years (n = 1560).

Assessments

Well-established semi-structured interview assessments were used to assess CHR criteria and symptoms[12,13]. The Schizophrenia Proneness Instrument (SPI)[15,16] was

used to assess the 14 BS included in the two BS CHR criteria and the criteria themselves (Table 1); in the BEAR study, the Adult version (SPI-A)[15] and, in the BEARS-Kid study, the Child and Youth version (SPI-CY)[16,52] was used. Both versions of the SPI do not differ in the definitions of corresponding BS and BS criteria. As in earlier studies[19,23-25], for the current analysis, cognitive and perceptual BS were distinguished rather than employ the partially overlapping criteria for BS (Table 1). Irrespective of their frequency of occurrence, perceptual BS included at least one visual or acoustic perception disturbance; and cognitive BS included thought interference, blockages, pressure, and perseveration, disturbances of receptive and expressive speech, of abstract thinking, and of discriminating between ideas and perceptions; captivation of attention by details of the visual field; inability to divide attention; unstable ideas of reference; and derealization. The SPI-CY requires a minimum age of 13 years for the assessment of three of the 14 BS included in COPER and COGDIS[16] (Table 1). For this reason, main analyses were conducted on the eleven BS assessed across all age groups to avoid a negative selection bias in the youngest age group, *i.e*., the 8- to 12-year-olds.

Furthermore, the five positive (P) items of the Structured Interview for Psychosis-Risk Syndromes (SIPS)[14] were used to explore the presentation of APS and brief intermittent psychotic symptoms (BIPS), and of the symptomatic UHR criteria (Table 1). More specifically, the current presentation of any APS (any SIPS item from P1 to P5 with a score between 3 and 5) and any BIPS (any SIPS item from P1 to P5 with a score of 6) was assessed. Delusional (P1, P2, and P3), hallucinatory (P4) and speech-disorganization (P5) APS/BIPS were distinguished irrespective of their frequency of occurrence. Of the genetic risk and deterioration syndrome (GRDS), a genetic risk was estimated only by a first-degree relative of psychosis. A schizotypal personality disorder in the participant was not assessed because of the lack of an informant[53] and the non-assessment of the negative schizotypal symptoms, which are part of the negative scale of the SIPS, in the BEAR study, and because of the young age of participants in the BEARS-Kid study.

Symptom-independent current global level of psychosocial functioning was estimated using the Social and Occupational Functioning Assessment Scale (SOFAS)[54]; a score ≤ 70 was considered indicative of low, *i.e*., clinically significant, impairment in functioning. The Mini-International Neuropsychiatric Interview (M.I.N.I.)[55] and its children's version (M.I.N.I. Kid)[56] were used to assess current axis I disorders according to DSM-IV and to rule out past or present psychosis. Again for the lack of an informant in the BEAR study[53] and for the young age in the BEARS-Kid study, axis II disorders were not assessed.

In addition, as part of the sociodemographic assessment, participants (or a parent, in 8- to 15-year-olds) were asked about first- and second-degree biological family members with mental problems, treated or untreated, and the diagnosis or, if unknown or never seeking help, a description of these problems (and treatment, if applicable).

In both the BEAR and the BEARS-Kid study, interviewers were clinical psychologists who had received an intensive three-month training, especially in the semi-structured context-dependent personalized assessment of CHR symptoms and mental disorders, in order to achieve a ≥ 95% concordance rate with the trainers (in all instances the first or the last author) before the conduction of interviews. Weekly supervision of all symptom ratings performed by the first or last author further ensured excellent, reliable data quality in both studies.

Statistical analysis

Using SPSS 25.0., frequencies were compared by χ^2 tests, and non-normally distributed interval and ordinal data were evaluated by Mann-Whitney tests. In accordance with other studies of age effects in CHR symptoms and criteria[19,23-25], logistic regression analyses were used to calculate (1) Simple effects of the seven age groups on prevalence rates of CHR symptoms and criteria; (2) Simple effects of sex on prevalence rates of CHR symptoms and criteria; (3) Interaction effects of age and sex on prevalence rates of CHR symptoms and criteria; and (4) The interaction effect of age, sex and the single CHR symptoms or criteria on low psychosocial functioning, and the presentation of at least one axis I disorder as dependent variables. To test the simple effects, we used the enter method. To test the interaction effects, we entered the single variables as well as all of their possible combinations of interactions and employed stepwise logistic regression analyses using both the backward and the forward selection to control for the different suppressor effects associated with each selection mode. Significant predictors that were selected in both searches were re-entered in a regression analysis using the enter method to estimate their model fit. Relevant interactions were inspected for their direction by interaction graphs. Throughout, goodness-of-fit was estimated by the Omnibus test.

In accordance with previous studies of age effects[19,23-25], the age group with a peak onset of first episode psychosis (20-24 years) served as a reference group in regression analyses of simple effects of age groups, while age rather than age group was entered in analyses of interactions because of the expected rather small numbers of low functioning and mental disorders per age group. Regarding sex, because of the reported higher incidence of psychotic disorders in men[6], females served as a reference group. There was no missing data.

RESULTS

Sample characteristics

The majority of our sample had a Swiss nationality, already concluded school education, good psychosocial functioning and a normal occupation (Table 2). The rare sex differences were of only small effect size (0.080-0.174), indicating a slight tendency of more men being single, and of more women working in temporary job, reporting a 1st- or 2nd-degree relative with mental disorder, mostly with an affective disorder, and meeting a current non-psychotic axis I disorder.

Prevalence of CHR symptoms and criteria

Altogether, 542 (18.6%) participants reported any CHR symptom; of these, 261 (9.0%) participants reported any one of the 11 BS and 381 (13.1%) any one of the five APS/BIPS, with only ten (0.35%) reporting BIPS (one delusional and nine hallucinatory) (Table 3). Speech-disorganization occurred only at APS-level and was extremely rare, not rated at all in 14- to 19-year-olds (Table 3).

Only 2.8% met criteria of any CHR criterion; mostly the BS criterion "Cognitive-Perceptive BS", COPER (2.2%) (Table 4). Thus, when only the three criteria recommended within the Guidance project of the European Psychiatric Association (EPA)[13], *i.e.*, APSS, the BIPS syndrome (BIPSS) and the BS criterion Cognitive Disturbances (COGDIS), were considered, only 1.3% met any EPA-recommended CHR criterion (henceforth: EPA criterion). Because of the lack of reporting a sufficient decline in functioning, despite some reports of a family history of psychotic disorders (Table 2), none of the participants met the GRDS (Table 4). Also, BIPSS was very rare, its requirements met by only one participant (Table 4).

Simple and combined effects of age and sex on CHR symptoms

Age effects indicated the same age thresholds for BS as reported earlier from a smaller subsample[25] (Tables 5-7), *i.e.*, a threshold of any BS and of cognitive BS in the first half of the twenties and of perceptual BS around age 18, whereby participants below these threshold had a higher likelihood to report BS and effects of age were most pronounced on cognitive BS. A newly emerging significant finding was the lower prevalence of perceptual BS in 30- to 40-year-olds. Overall, BS were significantly less frequent in males, with little differences between cognitive and perceptual BS (Tables 5-7).

Similar to earlier findings on a smaller subsample of the present sample[24], an age effect on the report of delusional APS/BIPS was hardly detectable, apart from a slightly increased prevalence in 30- to 40-year-olds (Table 8). In any APS/BIPS and in hallucinatory APS/BIPS (Tables 9 and 10), an age threshold around age 18 showed with an additional trend toward lesser hallucinatory APS/BIPS in 30- to 40-year-olds counteracting the age effect on delusional APS/BIPS in this age group; consequently, no age effect on any APS/BIPS emerged. Due to their rare occurrence (Table 3), no age effect was detectable on speech-disorganization APS (Table 11). Similar to the findings on BS, APS/BIPS were commonly less frequent in males (Tables 9-10); the only exception occurred in speech-disorganization APS that revealed a statistical trend towards being more frequent in males (Table 11).

Except for the age models on delusional and speech-disorganization APS/BIPS, all models indicated an improved model fit that, just like the explained variance, was commonly greater for the age group models compared to the sex models (Tables 5-11).

Except for delusional APS/BIPS that were only predicted by female sex (Table 8), both forward and backward selections indicated an effect of both age and sex on the report of CHR symptoms (Tables 12-17). In doing so, except for cognitive BS (Table 13), age and sex – if selected – were not only independent predictors but weakly interacted with each other (Tables 12, 14-17). Visual inspection of the interaction graphs revealed that, in case of any BS and perceptual BS, the likelihood of reporting these BS decreased with age in females, while it increased with age in males. Additionally, the presentation of both any and perceptual BS was generally more

Table 2 Sociodemographic and clinical characteristics of the sample

	Total sample (*n* = 2916)	Males (*n* = 1550)	Females (*n* = 1366)	χ^2(df)/U; *P* value (Cramer's V/Rosenthal's *r*)
Study participation: *n* (%) in BEAR	2683 (92.0)	1447 (93.4)	1236 (90.5)	8.14 (1); 0.004 (0.053)
Age in years: mean ± SD, Mdn	28.8 ± 8.7, 31	28.6 ± 8.6, 31	29.0 ± 8.9; 32	1031227.0; 0.226 (0.022)
Nationality: *n* (%) Swiss	2708 (92.9)	1433 (92.5)	1275 (93.3)	0.86 (1); 0.353 (0.017)
Marital status: *n* (%) single	1730 (59.3)	977 (63.0)	753 (55.1)	18.82 (1); < 0.001 (0.080)
Concluded school education: *n* (%) yes	2538 (87.0)	1372 (88.5)	1166 (85.4)	6.42 (1); 0.011 (0.047)
Highest school education: *n* (%)				5.14 (3); 0.162 (0.042)
ISCED 1	148 (5.1)	78 (5.0)	70 (5.1)	
ISCED 2	1689 (57.9)	921 (59.4)	768 (56.2)	
ISCED 3 (34+35)	1079 (37.0)	551 (35.6)	528 (38.7)	
Current occupation: *n* (%)				27.96 (4); < 0.001 (0.098)
Unemployed	61 (2.1)	37 (2.4)	24 (1.8)	
Sheltered work place	7 (0.2)	7 (0.5)	0	
Self-employed or temporary job, or other	34 (1.2)	6 (0.4)	28 (2.1)	
Normal occupation incl. education	2814 (96.5)	1500 (96.8)	1314 (96.2)	
1st- or 2nd-degree relative with mental disorder: *n* (%)[1]	1133 (39.0)	479 (31.0)	654 (48.1)	87.93 (1); < 0.001 (0.174)
With psychosis	89 (3.1)	34 (2.2)	55 (4.0)	8.22 (1); 0.004 (0.053)
With affective disorder	691 (23.8)	274 (17.8)	417 (30.6)	66.18 (1); < 0.001 (0.151)
Current SOFAS score: mean ± SD, Mdn	85.2 ± 7.1, 87	85.4 ± 7.3, 88	85.0 ± 6.9, 87	998335.5; 0.007 (0.050)
Highest-past-year SOFAS score: mean ± SD, Mdn	85.4 ± 6.9, 87	85.6 ± 7.0, 88	85.2 ± 6.8, 87	1002860.0; 0.013 (0.079)
Psychosocial impairment (SOFAS ≤ 70): *n* (%)	161 (5.5)	79 (5.1)	82 (6.0)	1.13 (1); 0.285 (0.020)
Current mental disorder: *n* (%)	386 (13.4)	158 (10.2)	228 (16.7)	26.69 (1); < 0.001 (0.096)

[1]Of *n* = 2904 with known biological relatives. BEAR: Bern Epidemiology At-Risk; SOFAS: Social and Occupational Functioning Assessment Scale.

likely at a younger age and in females, with sex having a greater effect than age. A similar interaction was found for speech-disorganization APS, yet, with positives cases being generally older than negative cases.

In case of any APS/BIPS and hallucinatory APS/BIPS, interaction graphs revealed a contrary pattern with the likelihood of reporting these APS/BIPS increasing with age in females and decreasing in males, both against the background of younger age being an independent predictor.

Simple and combined effects of age and sex on CHR criteria

Contrary to in CHR symptoms, the simple age group effect on CHR and EPA criteria indicated a lower prevalence in those of age 25 and older rather than a higher frequency in the younger age groups (Tables 18-19). Similar to the findings on CHR symptoms, however, females were more likely to report CHR or EPA criteria, again with sex explaining less variance than age groups (Tables 18, 19).

In the combined models, however, and once more in contrast to CHR symptoms, age and sex entered as independent predictors only, with younger age and female gender being associated with a higher likelihood of meeting any CHR or any EPA criterion (Tables 20-21). In doing so, sex was a stronger predictor compared to age (Tables 20, 21).

Effects of age, sex, and CHR symptoms and criteria on psychosocial impairment

With the exception of speech-disorganisation APS, for which different predictors were selected in forward and backward selection (*i.e.*, the APS in forward and the interaction of this APS with age in backward selection), age in interaction with the

Table 3 Frequency of clinical high risk symptoms in age groups and sexes, *n* (% of group)

	Any BS	Any cognitive BS	Any perceptual BS	Any APS or BIPS	Any delusional APS or BIPS	Any hallucinatory APS or BIPS	Any speech disorganization APS
8-12 yr	21 (17.9)	14 (12.0)	11 (9.4)	36 (30.8)	6 (5.1)	32 (27.4)	1 (0.9)
13-15 yr	18 (26.1)	15 (21.7)	5 (7.2)	15 (21.7)	4 (5.8)	14 (20.3)	0
16-17 yr	30 (15.7)	17 (8.9)	20 (10.5)	38 (19.9)	15 (7.9)	32 (16.8)	0
18-19 yr	27 (16.2)	19 (11.4)	9 (5.4)	27 (16.2)	9 (5.4)	21 (12.6)	0
20-24 yr	40 (8.1)	20 (4.1)	23 (4.7)	58 (11.8)	23 (4.7)	42 (8.5)	1 (0.2)
25-29 yr	23 (7.2)	12 (3.8)	11 (3.4)	33 (10.3)	15 (4.7)	22 (6.9)	2 (0.6)
30-40 yr	102 (6.5)	68 (4.4)	41 (2.6)	174 (11.2)	113 (7.2)	98 (6.3)	16 (1.0)
Male	110 (7.1)	69 (4.5)	51 (3.3)	161 (10.4)	79 (5.1)	107 (6.9)	15 (1.0)
Female	151 (11.1)	96 (7.0)	69 (5.1)	220 (16.1)	106 (7.8)	154 (11.3)	5 (0.4)
Total	261 (9.0)	165 (5.7)	120 (4.1)	381 (13.1)	185 (6.3)	261 (9.0)	20 (0.7)

BS: Basic symptom; BIPS: Brief intermittent psychotic symptoms; APS: Attenuated psychotic symptoms.

respective CHR symptom or criterion predicted psychosocial impairment (Tables 22-29). Only in case of perceptual BS, this interaction was further moderated by sex (Table 24).

Except for delusional APS/BIPS, the twofold interactions indicated that participants with no impairment were younger when they reported CHR symptoms or criteria compared to those not reporting these. This trend was similar but less pronounced for those with a psychosocial impairment in case of hallucinatory APS/BIPS, CHR criteria and EPA criteria, while it was opposite but less pronounced (*i.e.*, higher age in those with both social impairment, and CHR symptoms and criteria compared to those with only psychosocial impairment) in case of any BS, any cognitive BS and any APS/BIPS. In case of delusional APS/BIPS, both participants with and without psychosocial impairment were older when they reported delusional APS/BIPS compared to when they did not report delusional APS/BIPS, with this interaction being more pronounced in those with an impairment. In case of perceptual BS, the interaction effect between age and symptoms on psychosocial impairment was more pronounced in males, in whom this interaction was similar to that of age and symptoms in case of any or cognitive BS. In females, however, both participants with and without a social impairment were younger in the presence of perceptual BS, yet without the perceivable difference in the strength of this effect that was displayed in case of hallucinatory APS/BIPS, CHR criteria and EPA criteria, indicating an absence of an age-by-perceptual BS interaction in females.

Effects of age, sex, and CHR symptoms and criteria on nonpsychotic mental disorder

Contrary to its minor role in respect to psychosocial impairment, sex was always an independent predictor of the presentation of any non-psychotic axis-I disorder according to DSM-IV (Tables 30-38). Mostly, sex was a predictor in addition to the CHR symptoms or criteria without interacting with them, in doing so, playing a lesser role (Tables 32-35, 37, 38). It was even the sole predictor of mental illness in case of any BS (Table 30), likely because the additional role of cognitive BS but not of perceptual BS was moderated by age (Table 31), indicating that mental disorder was less likely when participants with cognitive BS were younger, while in participants with mental disorder, age did not differ between those with and without cognitive BS. The additional role of speech-disorganization APS was also moderated by age (Table 36); yet, other than in case of cognitive BS, indicating that, irrespective of the presentation of mental disorder, participants without this APS were commonly younger than those with it; this age effect being more pronounced in those with mental disorder. In both models, the one with cognitive BS and the one with speech-disorganization APS, the effect of sex was greater than the effect of the age-symptom interaction (Tables 31, 36).

DISCUSSION

Differential age thresholds in CHR symptoms were reported from a much smaller

Table 4 Frequency of clinical high risk criteria in age groups and sexes, *n* (% of group)

	Any CHR criterion	Any EPA criterion	COPER	COGDIS	APSS	BIPSS	GRDS, only by family history
8-12 yr	7 (6.0)	5 (4.3)	2 (1.7)	1 (0.9)	4 (3.4)	0	0
13-15 yr	5 (7.2)	4 (5.8)	3 (4.3)	3 (4.3)	1 (1.4)	0	0
16-17 yr	9 (4.7)	1 (0.5)	9 (4.7)	1 (0.5)	0	0	0
18-19 yr	5 (3.0)	3 (1.8)	4 (2.4)	3 (1.8)	1 (0.6)	0	0
20-24 yr	19 (3.9)	11 (2.2)	12 (2.4)	3 (0.6)	8 (1.8)	1 (0.2)	0
25-29 yr	4 (1.3)	1 (0.3)	3 (0.9)	0	1 (0.3)	0	0
30-40 yr	33 (2.1)	13 (0.8)	30 (1.9)	10 (0.6)	5 (0.3)	0	0
Male	29 (1.9)	13 (0.8)	22 (1.4)	6 (0.4)	9 (0.6)	0	0
Female	53 (3.9)	25 (1.8)	41 (3.0)	15 (1.1)	11 (0.8)	1 (0.1)	0
Total	82 (2.8)	38 (1.3)	63 (2.2)	21 (0.7)	20 (0.7)	1 (0.03)	0

CHR: Clinical high risk; EPA: European Psychiatric Association; COPER: Cognitive-Perceptive Basic Symptoms; COGDIS: Cognitive Disturbances; APSS: Attenuated Psychotic Symptoms Syndrome; BIPSS: Brief Intermittent Psychotic Symptoms Syndrome; GRDS: Genetic Risk and Deterioration Syndrome.

subsample (n = 689) of the present sample (n = 2916) in the community[24,25], suggesting an age threshold of about 15/16 year-of-age for APS that was subsequently supported in clinical samples[18,19]. An age threshold for perceptual BS around age of 18 years and an age threshold for cognitive BS within the first half of the twenties was found in the community[25]. In any case, a higher prevalence and lesser clinical relevance of the respective CHR symptoms in the age groups below these thresholds were observed[18,19,24,25]. In line with the BS concept[57,58] and current biological and cognitive behavioral models of psychosis[1,59,60], these age thresholds were interpreted as signaling a main relation of APS to the maturation of major cognitive skills and a main relation of BS to brain maturation[25]. Furthermore, because of the sex differences in brain and cognitive maturation[44-47], and likely, in symptomatology associated with psychosis and the CHR states[30-39], it was anticipated that sex and age might interact, thus leading to lower age thresholds in the prevalence and clinical significance of BS and possibly APS in females compared to males[25]. Hence, in our highly original study, we investigated the effects of age and sex on the prevalence of CHR criteria and symptoms and on their association with psychosocial impairment and mental ill-health in a large community sample of 8- to 40-year-olds. Overall, our results supported the influence of both age and sex on the presentation and clinical relevance of CHR symptoms and criteria; yet, these somewhat differed in their relation to CHR symptoms and criteria, and greatly differed in their interplay with CHR symptoms and criteria in relation to proxy measures of the clinical relevance, *i.e.*, presentation of psychosocial functional impairment and non-psychotic axis I mental disorder according to DSM-IV.

Age, sex and perception-related CHR symptoms

With regard to the simple effects of age and sex, the age thresholds in BS reported from an earlier subsample[25], including the missing significance of perceptual BS in the smallest age group of 13- to 15-year-olds (n = 69), was confirmed. Related to the higher power in the present much larger sample compared to the earlier smaller subsample, all reported age group effects now reached level of significance. Newly, this was also the case for a lower prevalence of perceptual BS in the largest age group of 30- to 40-year-olds (n = 1560), which might indicate a continuous slow decrease with age rather than a strict age threshold in perceptual BS. Future community studies with larger samples of younger age groups or studies on clinical samples with a higher prevalence of perceptual BS are needed to decide between an age threshold related to brain maturation processes and a slow decrease in perceptual BS. A slow decrease might reflect continuously strengthened top-down processes in perception, which had been related to the longer duration of the schizophrenia prodrome with perceptual BS[61].

For hallucinatory APS/BIPS, similar age group effects showed but were more pronounced for the three young age groups and less pronounced for the 30- to 40-year-olds. Thus, in contrast to the earlier analyses of a smaller subsample of the present sample, no difference in age thresholds between perceptual BS and hallucinatory APS/BIPS was found. Symptom capture studies, in particular of auditory hallucinations, indicated a pattern of increased coupling among the auditory, language and striatal regions, while resting state studies suggest that the default mode network might be involved in both auditory and visual

Table 5 Simple effects of age group and sex on presence of ≥ 1 of the 11 basic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age category			64.146	6	0.000			
8-12 yr	0.907	0.292	9.655	1	0.002	2.477	1.398	4.390
13-15 yr	1.386	0.320	18.753	1	0.000	3.997	2.135	7.483
16-17 yr	0.747	0.258	8.355	1	0.004	2.110	1.272	3.501
18-19 yr	0.781	0.267	8.549	1	0.003	2.184	1.294	3.687
25-29 yr	-0.128	0.272	.221	1	0.639	0.880	0.516	1.500
30-40 yr	-0.233	0.194	1.438	1	0.230	0.792	0	1.159
Sex								
Male	-0.487	0.131	13.747	1	0.000	0	0.475	0.795

Reference groups are 20-24-year-olds and females, respectively. Age: GoF: $\chi^2(6) = 58.10$; $P < 0.001$; Nagelkerke's $R^2 = 0.044$. Sex: GoF: $\chi^2(1) = 13.94$; $P < 0.001$; Nagelkerke's $R^2 = 0.011$.

hallucinations[87]. Further, next to these neurobiological findings, also unstable memories, impaired source monitoring, and poor top-down attention were suggested to play a role in the formation of hallucinations[62,63].

Thus, age group effects indicate that brain maturation processes, in particular of temporal and occipital regions, might play a role in the occurrence of both perceptual BS and hallucinatory BS, with sex-dependent maturation of cognitive abilities[45,64,65] such as memory, source monitoring and top-down attention further impacting on the appraisal, and thereby the severity of hallucinatory experiences. While this might explain the age group effects, it does not explain the simple sex findings, with higher prevalence rates in females. However, the interaction of age and sex in perceptual BS and hallucinatory APS/BIPS indicated that, in line with our initial assumption, in particular younger females were prone to report perceptual BS, whereas, contrary to our expectations, hallucinatory APS/BIPS were more frequently reported by females with advancing age. Thus, brain maturation processes might be more pronounced in perceptual BS that, for this reason, are also independently influenced by sex, while sex differences in neurocognitive mechanisms might further moderate hallucinatory experiences, thereby protecting hallucination-prone females for some time. However, to better understand age and sex effects in perception-related CHR symptoms more research employing both sophisticated neurobiological and psychopathological assessments are needed[66].

Age, sex and cognition-related CHR symptoms

Compared to perceptual BS, more pronounced effects of age group and, relatedly, a more distinct age threshold showed for cognitive BS, which was also indicated by a higher amount of explained variance (39% for perceptual *vs* 47% for cognitive BS). This supports the earlier notion of cognitive BS being related to brain maturation processes, particularly of frontal regions[28]. As in earlier studies[24,19], the regression model of delusional APS/BIPS was not significant and revealed little effects of age on prevalence of delusional APS/BIPS, except for a newly detectable marginally significant effect in 30- to 40-year-olds, indicating a higher prevalence [Exp[Beta]=1.57 (1.01-2.53)]. In the earlier less powered study[24], however, an increased prevalence was also indicated in this age group by exhibiting the smallest *P* value that, however, had not even approached a statistical trend ($P = 0.19$; Exp[Beta]=1.82 (0.74-4.48))[24].

Interestingly, although no significant age model was detected for the newly separately considered speech-disorganization APS, the result also pointed towards a slightly higher prevalence in the 30- to 40-year-olds [$P = 0.114$; Exp[Beta]=5.10 (0.67-38.54)], despite the low number of altogether only 20 participants scoring positively on it. This age effect was again apparent in the mental disorder model including speech-disorganization APS; in which, in addition to female sex being related to mental disorders, older age was associated with the presence of speech-disorganization APS, in particular in those with mental disorder. Thus the interaction of age and speech-disorganization APS contributed to the prediction of mental disorders, though less than sex alone. Accordingly, contrary to all other associations between CHR symptoms and criteria, males were more likely to display speech-disorganization APS. These findings are somewhat in line with brain studies on cognitive and language functions, and their brain structure and function that reported a larger effect of sex compared to age[64,67-69] with little interaction between the two. A link of disturbed white matter in the cerebral language pathways with disorganized

Table 6 Simple effects of age group and sex on presence of ≥ 1 of the 9 cognitive basic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age category			56.279	6	0			
8-12 yr	1.168	0.365	10.233	1	0.001	3.215	1.572	6.574
13-15 yr	1.882	0.371	25.809	1	0.000	6.569	3.178	13.581
16-17 yr	0.838	0.342	6.011	1	0.014	2.311	1.183	4.513
18-19 yr	1.111	0.334	11.062	1	0.001	3.036	1.578	5.842
25-29 yr	-0.079	0.372	0.045	1	0.833	0.924	0.446	1.918
30-40 yr	0.075	0.260	0.083	1	0.773	1.078	0.648	1.794
Sex								
Male	-0.484	0.162	8.881	1	0.003	0.616	0.448	0.847

Reference groups are 20-24-year-olds and females, respectively. Age: GoF: $\chi^2(6) = 48.55$; $P < 0.001$; Nagelkerke's $R^2 = 0.047$. Sex: GoF: $\chi^2(1) = 9.02$; $P = 0.003$; Nagelkerke's $R^2 = 0.009$.

speech and formal thought disorder, respectively, in schizophrenia was suggested by findings of structural abnormalities predominantly in the left superior temporal gyrus, angular gyrus, inferior operculum and orbitofrontal cortex, and of functional abnormalities in the left superior and middle temporal gyrus[70-75]. These studies on clinical samples used clinical ratings or speech-samples to evaluate degree of disorganized speech, while the studies of age and sex effects on brain structures and functions in non-clinical samples commonly used objective neurocognitive measures[64,69]. These neurocognitive assessments commonly correlate to a small-to-moderate degree with speech disorganization[76]; thus, the age and sex effects reported in non-clinical samples might apply as well – an assumption further supported by our findings.

Other than observable speech disorganization, cognitive BS did not correlate to neurocognitive measures[77]. And contrary to speech-disorganization APS but similar to all other CHR symptoms and criteria, cognitive BS were related to female sex and most prevalent in younger age groups, in which age and sex acted independent of each other, with sex having a more pronounced impact on the report of cognitive BS. Furthermore, report of cognitive BS was increasingly related to functional impairment and presentation of a mental disorder with advancing age, in doing so exhibiting a divergent model for mental disorders compared to speech-disorganization APS, although female sex was related to mental disorders in both models. By definition, cognitive BS are spontaneously and immediately recognized as disturbances of one's own cognitive processes that differ from what is considered to be the "normal" mental self, and are not necessarily observable by others in terms of odd thinking, disturbed speech, or formal thought disorder[15,16,57,58]. For these phenomenological differences, cognitive BS formed a single factor in a recent dimensional analysis, while speech-disorganization APS joined other disorganization symptoms in a different factor; in doing so, the cognitive BS factor was positively linked to the disorganized factor and possibly acted as a facilitator[78]. With regards to the neurobiological underpinnings of cognitive BS, targeted studies are still missing[58] but, for the described differences to speech-disorganization APS, can be assumed to partly differ from those on formal thought disorders, especially with regard to the language-unrelated cognitive BS.

Sex and prevalence of APS/BIPS

With regard to sex, based on prevalence data on psychoses, we had expected more males to report CHR symptoms, in particular APS/BIPS, yet, this only showed at statistical trend level for speech-disorganization APS that were almost three times more frequent in men compared to females. In line with the literature on CHR samples and samples referred to specialized early detection services[20,31,34,36,38], more severe APS/BIPS, and more cognitive and perceptual BS were reported in females. This difference between more males within our studied age range presenting with frank psychotic disorder and more females presenting with CHR symptoms, might be related to differences in symptomatic sex effects in referral and converter samples of early detection services, and relatedly, in psychosis-specificity of sex effects[65]. Sex effects in referral or baseline APS/BIPS samples, both with an assumable high rate of non-conversion of at least 60%[13], were argued to reflect more general sex effects on psychopathology that included more frequent and/or severe positive psychotic symptoms (especially paranoid) in females[26,28,29]. This was also reported for some

Table 7 Simple effects of age group and sex on presence of ≥ 1 of the 2 perceptual basic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age category			35.620	6	0.000			
8-12 yr	0.752	0.382	3.872	1	0.049	2.121	1.003	4.484
13-15 yr	0.468	0.511	0.838	1	0.360	1.596	0.586	4.347
16-17 yr	0.871	0.319	7.483	1	0.006	2.390	1.280	4.462
18-19 yr	0.152	0.404	0.141	1	0.707	1.164	0.528	2.568
25-29 yr	-0.315	0.374	0.710	1	0.400	0.730	0.351	1.519
30-40 yr	-0.595	0.266	5.011	1	0.025	0.552	0.328	0.929
Sex								
Male	-0.447	0.189	5.623	1	0.018	0.640	0.442	0.925

Reference groups are 20-24-year-olds and females, respectively. Age: GoF: $\chi^2(6) = 32.82$; $P < 0.001$; Nagelkerke's $R^2 = 0.039$. Sex: GoF: $\chi^2(1) = 5.70$; $P = 0.017$; Nagelkerke's $R^2 = 0.007$.

CHR samples[31], though rather with respect to hallucinatory than to delusional APS/BIPS[34,38]. The working of more general sex effects – that impacts on the prevalence rates of mental disorders and their age of first presentation and is considered important for the understanding of causal mechanisms[79,80] – also has to be expected in our community sample and, consequently, might explain the higher prevalence of CHR symptoms in females.

A higher prevalence of APS in females with a very similar Exp[Beta] (or Odds Ratio) as found in our study [0.63 (0.42–0.93) *vs* 0.60 (0.49-0.75)] was recently reported from a Brazilian convenience sample of 6- to 14-year-olds from the community[39]. Yet, in this study, the prevalence rate of APS as assessed with Comprehensive Assessment of At-Rik Mental States (CAARMS)[81] was only 5.7%, and thus, much lower than our 13.1%-rate. In the Brazilian study, however, clinical relevance defined as "would raise concern about the child's mental health status in a clinical setting"[39] was emphasized, and more than three quarters of children fulfilled this criterion. While the CAARMS differs from the SIPS in the frequency and onset criteria, APS/BIPS cover largely the same phenomena in both assessments that both rate symptom severity at a 7-point scale with APS/BIPS being rated with a score of "≥ 3"[82]. In the CAARMS, a score of "5" requires "may result in some change in behaviour, but minor" for delusional APS, which is not required in scores of "3" and "4". A score of "4" only requires "Able to give plausible explanation for experience. May be associated with mild distress." For hallucinatory APS/BIPS, scoring thresholds are similarly high for impact on behaviour and conviction. Thus milder, easily dismissed, non-distressing experiences at the level of APS that did not impact on behaviour, and, consequently, likely would not raise concerns about the mental state (*i.e.*, lower CAARMS scores and, likewise, lower SIPS scores[82]), might not have been rated in the Brazilian study[39]. Except for the rarely rated grandiose ideas ($n = 8$), a score of "3" in the SIPS accounted for 60.0% to 72.3% of APS/BIPS-ratings in the remaining four P-items of the SIPS in our sample. Thus, this possible difference in scoring might account for some of the difference in prevalence rates of these two community studies. Furthermore, for developmental reasons, hallucinatory experiences that had the highest prevalence of APS in our sample might not be reliable assessable in 6- and 7-year-old children[17,83], and consequently, not rated in the Brazilian sample, this further decreasing the overall prevalence rate of APS.

Age, sex and CHR criteria

CHR criteria, at prevalence rates of 2.8% for any CHR and 1.3% for any EPA criterion, were far more infrequent compared to CHR symptoms, indicating that CHR symptoms are frequently not meeting onset and frequency requirements of CHR criteria (Table 1), mostly by infrequent occurrence[24,26,48,49]. Similar to the majority of CHR symptoms, CHR and EPA-recommended CHR criteria exhibited effects of both age and sex, with age group effects explaining more variance than sex effects. Different to most CHR symptoms, however, the age thresholds for CHR and EPA criteria around age of 24/25 years were higher and indicated a significantly lower prevalence above this age rather than a higher prevalence below it. In line with these effects of age groups, the combined analyses of age and sex indicated independent effects of these with younger age and, more pronounced, female sex being associated with meeting the criteria. This slightly higher age threshold might indicate that, in case of the above discussed aberrant processes in both neurocognitive and

Table 8 Simple effects of age group and sex on presence of ≥ 1 of the 5 attenuated psychotic symptoms or brief intermittent psychotic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age category			50.070	6	0.000			
8-12 yr	1.204	0.244	24.295	1	0.000	3.333	2.065	5.380
13-15 yr	0.734	0.324	5.144	1	0.023	2.083	1.105	3.928
16-17 yr	0.622	0.229	7.386	1	0.007	1.863	1.189	2.917
18-19 yr	0.369	0.252	2.138	1	0.144	1.446	0.882	2.372
25-29 yr	-0.145	0.231	0.392	1	0.531	0.865	0.550	1.361
30-40 yr	-0.060	0.161	0.139	1	0.709	0.942	0.686	1.292
Sex								
Male	-0.505	0.111	20.613	1	0.000	0.604	0.486	0.751

Reference groups are 20-24-year-olds and females, respectively. Age: GoF: $\chi^2(6) = 45.17$; $P < 0.001$; Nagelkerke's $R^2 = 0.028$. Sex: GoF: $\chi^2(1)=20.89$; $P < 0.001$; Nagelkerke's $R^2=0.013$.

neurobiological maturation, maturation disturbances underlying CHR symptoms have to persist and possibly increase before impacting sufficiently on psychopathology to meet CHR criteria[25,46,84].

Age, sex and clinical relevance of CHR symptoms and criteria

Our study confirmed the clinical relevance of CHR symptoms and criteria in terms of being selected as a predictor of both functional impairment and mental disorder, which were used as proxy measures of clinical relevance. Furthermore, it confirmed the earlier reported stronger association of CHR symptoms and criteria with functional impairment in comparison to mental disorder[49], in terms of larger explained variance of the functional impairment models compared to the corresponding mental disorder models. This indicates that CHR symptoms and criteria possess clinical relevance in themselves and are not merely a global indicator of mental ill-health[49,85].

A most striking global difference emerged with respect to the interplay of sex, age, and CHR symptoms and criteria in association to these two proxy measures of clinical relevance. Social impairment was commonly predicted by the interaction between age, and CHR symptoms and criteria, with only perceptual BS being additionally moderated by sex. In doing so, in all CHR symptoms but delusional APS/BIPS as well as in CHR/EPA criteria, younger age in the presence of CHR symptoms and criteria was associated with good psychosocial functioning. With regard to the mental disorder models, CHR symptoms and criteria and, to a lesser degree, sex were commonly independent predictors of mental disorders, with only cognitive BS and speech-disorganization APS being additionally moderated by age; in doing so, the interaction was a weaker predictor compared to sex. The role of sex indicated in all instances more females with current non-psychotic mental disorders. This sex effect in point-prevalence of mental disorders is in line with higher 12-month point but not lifetime prevalence rates of mental disorders in females[86], and is very likely independent of the effects of CHR symptoms and criteria. Follow-up of the sample will demonstrate in future to what degree CHR symptoms and, more importantly, CHR and EPA criteria are related to the development of psychotic and psychosis-spectrum disorders.

Strengths and limitations

Our study has several strengths and limitations. A clear strength of our study is the large sample size – albeit the disproportionate subsample sizes with lesser children and adolescents compared to adults, that must be considered a limitation. Another strength is the assessment of CHR symptoms and criteria in a way as done in clinical samples, *i.e.*, using standard instruments for the assessment of CHR states, carried out by well-trained and supervised clinical psychologists in clinical semi-structured interviews. Although this was done via the telephone in the BEAR study and face-to-face in the BEAR-Kid study, an earlier feasibility study that had compared telephone and face-to-face assessment of CHR symptoms and criteria in a fully crossed design reported good correspondence between this two assessment modes, especially when only focussing on presentation of CHR symptoms and criteria[50] as done in the present study. Thus, the reported differences between children and adolescents and adults, *i.e.*, the effects of age, are likely genuine and not only caused by an assessment

Table 9 Simple effects of age group and sex on presence of ≥ 1 of the 3 delusional attenuated psychotic symptoms or brief intermittent psychotic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age category			7.120	6	0.310			
8-12 yr	0.099	0.470	0.045	1	0.833	1.105	0.439	2.777
13-15 yr	0.229	0.558	0.169	1	0.681	1.258	0.422	3.751
16-17 yr	0.555	0.343	2.610	1	0.106	1.742	0.888	3.414
18-19 yr	0.152	0.404	0.141	1	0.707	1.164	0.528	2.568
25-29 yr	0.008	0.340	0.001	1	0.981	1.008	0.518	1.963
30-40 yr	0.467	0.235	3.961	1	0.047	1.596	1.007	2.529
Sex								
Male	-0.449	0.154	8.548	1	0.003	0.638	0.473	0.862

Reference groups are 20-24-year-olds and females, respectively. Age: GoF: $\chi^2(6) = 7.48$; $P = 0.279$; Nagelkerke's $R^2 = 0.007$. Sex: GoF: $\chi^2(1) = 8.66$; $P < 0.001$; Nagelkerke's $R^2 = 0.008$.

bias.

Albeit the similar recruitment procedure in the BEAR and the BEARS-Kid study that was based on random sampling from the population register, the lower response rate in the BEARS-Kid study might limit its representativeness. The BEAR sample, however, was already reported to be well-representative[49].

Despite the large sample size, however, some CHR symptoms and criteria occurred in too small numbers to meet the minimum of five outcome events per predictor variable in all regression analyses[87]. Regression analyses were consequently affected by this, in particular, simple age group effects as well as combined effects of age, sex, and CHR symptoms and criteria on the presentation of psychosocial impairment and of mental disorders in case of speech-disorganization APS, and also regression analyses on simple age effects in case of EPA criteria. Thus, these results might be of limited reliability and should be considered only with caution.

Earlier studies had only distinguished hallucinatory APS/BIPS from delusional and speech-disorganization APS/BIPS[19,23,24]. Thus, in light of the unique findings on speech-disorganization APS that fit well to the findings on cognitive BS, the separate consideration of delusional and speech-disorganization APS/BIPS can be regarded as another strength of our study.

Conclusion

Our results on a community sample indicate that age and sex impact on the prevalence of CHR symptoms and criteria as well as on their association with proxy measures of clinical relevance, *i.e.*, the presentation of functional impairment and of non-psychotic mental disorder. In doing so, age and sex moderate CHR symptoms and criteria in various ways, these differences opening ways to better understand their causal pathways. Thus, further efforts at unravelling causal pathways of psychosis, at biomarker discovery and at early therapeutic intervention should consider effects of both sex and age[17,24,25,46,84].

Table 10 Simple effects of age group and sex on presence of hallucinatory attenuated psychotic symptoms or brief intermittent psychotic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age category			80.886	6	0.000			
8-12 yr	1.397	0.263	28.262	1	0.000	4.043	2.415	6.766
13-15 yr	1.006	0.340	8.744	1	0.003	2.733	1.404	5.323
16-17 yr	0.771	0.252	9.343	1	0.002	2.161	1.318	3.542
18-19 yr	0.435	0.284	2.348	1	0.125	1.545	0.886	2.693
25-29 yr	-0.229	0.274	0.700	1	0.403	0.795	0.465	1.360
30-40 yr	-0.329	0.192	2.929	1	0.087	0.720	0.494	1.049
Sex								
Male	-0.539	0.132	16.711	1	0.000	0.584	0.451	0.756

Reference groups are 20-24-year-olds and females, respectively. Age: GoF: $\chi^2(6) = 72.42$; $P < 0.001$; Nagelkerke's $R^2 = 0.054$. Sex: GoF: $\chi^2(1) = 17.02$; $P < 0.001$; Nagelkerke's $R^2 = 0.013$.

Table 11 Simple effects of age group and sex on presence of speech-disorganization attenuated psychotic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age category			2.777	6	0.836			
8-12 yr	1.445	1.418	1.038	1	0.308	4.241	0.263	68.311
13-15 yr	-15.004	4838.665	0.000	1	0.998	0.000	0.000	.
16-17 yr	-15.004	2908.261	0.000	1	0.996	0.000	0.000	.
18-19 yr	-15.004	3110.226	0.000	1	0.996	0.000	0.000	.
25-29 yr	1.133	1.227	0.852	1	0.356	3.104	0.280	34.375
30-40 yr	1.629	1.032	2.491	1	0.114	5.098	0.674	38.543
Sex								
Male	0.978	0.518	3.570	1	0.059	2.660	0.964	7.338

Reference groups are 20-24-year-olds and females, respectively. Age: GoF: $\chi^2(6) = 10.57$; $P = 0.103$; Nagelkerke's $R^2 = 0.046$. Sex: GoF: $\chi^2(1) = 4.08$; $P = 0.044$; Nagelkerke's $R^2 = 0.018$.

Table 12 Combined effects of selected age and sex predictors on presence of ≥ 1 of the 11 basic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age	-0.062	0.009	42.503	1	0.000	0.940	0.923	0.958
Sex	-1.450	0.416	12.181	1	0.000	0.235	0.104	0.529
Age and sex	0.036	0.015	5.887	1	0.015	1.036	1.007	1.067

Reference group of sex is females. GoF: $\chi^2(3) = 62.40$; $P < 0.001$; Nagelkerke's $R^2 = 0.047$.

Table 13 Combined effects of selected age and sex predictors on presence of ≥ 1 of the 9 cognitive basic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age	-0.046	0.009	26.592	1	0.000	0.955	0.939	0.972
Sex	-0.496	0.163	9.250	1	0.002	0.609	0.442	0.838

Reference group of sex is females. GoF: $\chi^2(2) = 35.47$; $P < 0.001$; Nagelkerke's $R^2 = 0.034$.

Table 14 Combined effects of selected age and sex predictors on presence of ≥ 1 of the 2 perceptual basic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age	-0.078	0.014	32.110	1	0.000	0.925	0.901	0.950
Sex	-1.971	0.580	11.556	1	0.001	0.139	0.045	0.434
Age and sex	0.060	0.021	7.893	1	0.005	1.062	1.018	1.107

Reference group of sex is females. GoF: $\chi^2(3) = 40.47$; $P < 0.001$; Nagelkerke's $R^2 = 0.047$.

Table 15 Combined effects of selected age and sex predictors on presence of ≥ 1 of the 5 attenuated psychotic symptoms or brief intermittent psychotic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age	-0.024	0.006	14.923	1	0.000	0.976	0.964	0.988
Age and sex	-0.019	0.004	21.891	1	0.000	0.982	0.974	0.989

Reference group of sex is females. GoF: $\chi^2(2) = 48.37$; $P < 0.001$; Nagelkerke's $R^2 = 0.030$.

Table 16 Combined effects of selected age and sex predictors on presence of hallucinatory attenuated psychotic symptoms or brief intermittent psychotic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age	-0.047	0.007	40.904	1	0.000	0.954	0.940	0.968
Age and sex	-0.022	0.005	18.547	1	0.000	0.978	0.969	0.988

Reference group of sex is females. GoF: $\chi^2(2) = 77.65$; $P < 0.001$; Nagelkerke's $R^2 = 0.058$.

Table 17 Combined effects of selected age and sex predictors on presence of speech-disorganization attenuated psychotic symptoms

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age and sex	0.047	0.016	8.505	1	0.004	1.048	1.016	1.082

Reference group of sex is females. GoF: $\chi^2(1)=9.85$; $P = 0.002$; Nagelkerke's $R^2 = 0.043$.

Table 18 Simple effects of age group and sex on presence of ≥ 1 clinical high risk criterion

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age category			17.714	6	0.007			
8-12 yr	0.462	0.455	1.034	1	0.309	1.588	0.651	3.870
13-15 yr	0.667	0.520	1.647	1	0.199	1.949	0.703	5.400
16-17 yr	0.210	0.414	0.257	1	0.612	1.234	0.548	2.777
18-19 yr	-0.261	0.511	0.262	1	0.609	0.770	0.283	2.095
25-29 yr	-1.150	0.555	4.291	1	0.038	0.317	0.107	0.940
30-40 yr	-0.618	0.293	4.453	1	0.035	0.539	0.304	0.957
Sex								
Male	-0.750	0.234	10.272	1	0.001	0.472	0.299	0.747

Reference groups are 20-24-year-olds and females, respectively. Age: GoF: $\chi^2(6) = 17.23$; $P = 0.008$; Nagelkerke's $R^2 = 0.026$. Sex: GoF: $\chi^2(1) = 10.79$; $P = 0.001$; Nagelkerke's $R^2 = 0.016$.

Table 19 Simple effects of age group and sex on presence of ≥ 1 European Psychiatric Association-recommended clinical high risk criterion

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age category			22.230	6	0.001			
8-12 yr	0.671	0.549	1.491	1	0.222	1.956	0.666	5.743
13-15 yr	0.992	0.599	2.746	1	0.098	2.697	0.834	8.717
16-17 yr	-1.467	1.048	1.960	1	0.162	0.231	0.030	1.799
18-19 yr	-0.221	0.658	0.113	1	0.737	0.802	0.221	2.908
25-29 yr	-1.982	1.047	3.584	1	0.058	0.138	0.018	1.073
30-40 yr	-0.999	0.413	5.852	1	0.016	0.368	0.164	0.827
Sex								
Male	-0.790	0.344	5.279	1	0.022	0.454	0.231	0.890

Reference groups are 20-24-year-olds and females, respectively. Age: GoF: $\chi^2(6) = 21.65$; $P = 0.001$; Nagelkerke's $R^2 = 0.057$. Sex: GoF: $\chi^2(1) = 5.60$; $P = 0.018$; Nagelkerke's $R^2 = 0.015$.

Table 20 Combined effects of selected age and sex predictors on presence of ≥ 1 clinical high risk criterion

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age	-0.043	0.012	12.101	1	0.001	0.958	0.935	0.982
Sex	-0.760	0.235	10.511	1	0.001	0.468	0.295	0.740

Reference group of sex is females. GoF: $\chi^2(2) = 22.75$; $P < 0.001$; Nagelkerke's $R^2 = 0.034$.

Table 21 Combined effects of selected age and sex predictors on presence of ≥ 1 European Psychiatric Association-recommended clinical high risk criterion

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age	-0.055	0.018	9.480	1	0.002	0.946	0.914	0.980
Sex	-0.799	0.345	5.372	1	0.020	0.450	0.229	0.884

Reference group of sex is females. GoF: $\chi^2(2) = 15.08$; $P = 0.001$; Nagelkerke's $R^2 = 0.040$.

Table 22 Combined effects of selected age, sex and symptoms (≥ 1 of 11 basic symptoms) predictors on presence of psychosocial impairment (Social and Occupational Functioning Assessment Scale ≤ 70)

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age and BS	0.051	0.006	62.374	1	0.000	1.052	1.039	1.066

GoF: $\chi^2(1) = 49.21$; $P < 0.001$; Nagelkerke's $R^2 = 0.048$. BS: Basic symptom.

Table 23 Combined effects of selected age, sex and symptoms (≥ 1 of 9 cognitive basic symptoms) predictors on presence of psychosocial impairment (Social and Occupational Functioning Assessment Scale ≤ 70)

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age and BS	0.055	0.007	54.240	1	0.000	1.056	1.041	1.072

GoF: $\chi^2(1) = 41.41$; $P < 0.001$; Nagelkerke's $R^2 = 0.041$. BS: Basic symptom.

Table 24 Combined effects of selected age, sex and symptoms (≥ 1 of 2 perceptual basic symptoms) predictors on presence of psychosocial impairment (Social and Occupational Functioning Assessment Scale ≤ 70)

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age and sex and BS	0.062	0.011	31.588	1	0.000	1.064	1.041	1.087

Reference group of sex is females. GoF:$\chi^2(1) = 23.36$; $P < 0.001$; Nagelkerke's $R^2 = 0.023$. BS: Basic symptom.

Table 25 Combined effects of selected age, sex and symptoms (≥ 1 of 5 attenuated psychotic symptoms/brief intermittent psychotic symptoms) predictors on presence of psychosocial impairment (Social and Occupational Functioning Assessment Scale ≤ 70)

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age and APS	-0.043	0.012	12.101	1	0.001	0.958	0.935	0.982

GoF: $\chi^2(1) = 113.70$; $P < 0.001$; Nagelkerke's $R^2 = 0.110$. APS: Attenuated psychotic symptoms.

Table 26 Combined effects of selected age, sex and symptoms (≥ 1 of 3 delusional attenuated psychotic symptoms/brief intermittent psychotic symptoms) predictors on presence of psychosocial impairment (Social and Occupational Functioning Assessment Scale ≤ 70)

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age and APS	0.064	0.006	117.318	1	0.000	1.066	1.054	1.079

GoF: $\chi^2(1)=91.82$; $P < 0.001$; Nagelkerke's $R^2 = 0.089$. APS: Attenuated psychotic symptoms.

Table 27 Combined effects of selected age, sex and symptoms (hallucinatory attenuated psychotic symptoms/brief intermittent psychotic symptoms) predictors on presence of psychosocial impairment (Social and Occupational Functioning Assessment Scale ≤ 70)

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age and APS	0.048	0.007	51.014	1	0.000	1.049	1.035	1.063

GoF: $\chi^2(1) = 40.25$; $P < 0.001$; Nagelkerke's $R^2 = 0.039$. APS: Attenuated psychotic symptoms.

Table 28 Combined effects of selected age, sex and criteria (≥ 1 clinical high risk criterion) predictors on presence of psychosocial impairment (Social and Occupational Functioning Assessment Scale ≤ 70)

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age and CHR criterion	0.091	0.009	100.738	1	0.000	1.095	1.076	1.115

GoF: $\chi^2(1) = 84.42$; $P < 0.001$; Nagelkerke's $R^2 = 0.082$. CHR: Clinical high risk.

Table 29 Combined effects of selected age, sex and criteria (≥ 1 European Psychiatric Association criterion) predictors on presence of psychosocial impairment (Social and Occupational Functioning Assessment Scale ≤ 70)

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Age and EPA criterion	0.107	0.014	57.021	1	0.000	1.113	1.083	1.145

GoF: $\chi^2(1) = 55.71$; $P < 0.001$; Nagelkerke's $R^2 = 0.054$. EPA: European Psychiatric Association.

Table 30 Combined effects of selected age, sex and symptoms (≥ 1 of 11 basic symptoms) predictors on presence of any non-psychotic axis-I disorder

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Sex	-0.568	0.111	26.224	1	0.000	0.567	0.456	0.704

Reference group of sex is females. GoF: $\chi^2(1) = 26.69$; $P < 0.001$; Nagelkerke's $R^2 = 0.017$.

Table 31 Combined effects of selected age, sex and symptoms (≥ 1 of 9 cognitive basic symptom) predictors on presence of any non-psychotic axis-I disorder

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Sex	-0.547	0.112	23.953	1	0.000	0.579	0.465	0.720
Age and BS	0.039	0.006	35.956	1	0.000	1.039	1.026	1.053

Reference group of sex is females. GoF: $\chi^2(2) = 58.03$; $P < 0.001$; Nagelkerke's $R^2 = 0.036$. BS: Basic symptom.

Table 32 Combined effects of selected age, sex and symptoms (≥ 1 of 2 perceptual basic symptoms) predictors on presence of any non-psychotic axis-I disorder

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Sex	-0.547	0.112	23.963	1	0.000	0.579	0.465	0.721
BS	1.135	0.206	30.355	1	0.000	3.112	2.078	4.660

Reference group of sex is females. GoF: $\chi^2(2) = 53.03$; $P < 0.001$; Nagelkerke's $R^2 = 0.033$. BS: Basic symptom.

Table 33 Combined effects of selected age, sex and symptoms (≥ 1 of 5 attenuated psychotic symptoms/brief intermittent psychotic symptoms) predictors on presence of any non-psychotic axis-I disorder

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Sex	-0.488	0.113	18.482	1	0.000	0.614	0.492	0.767
APS	1.318	0.129	104.567	1	0.000	3.735	2.902	4.809

Reference group of sex is females. GoF: $\chi^2(2) = 121.11$; $P < 0.001$; Nagelkerke's $R^2 = 0.075$. APS: Attenuated psychotic symptoms.

Table 34 Combined effects of selected age, sex and symptoms (≥ 1 of 3 delusional attenuated psychotic symptoms/brief intermittent psychotic symptoms) predictors on presence of any non-psychotic axis-I disorder

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Sex	-0.528	0.113	21.963	1	0.000	0.590	0.473	0.735
APS	1.442	0.165	76.391	1	0.000	4.230	3.061	5.845

Reference group of sex is females. GoF: $\chi^2(2) = 93.44$; $P < 0.001$; Nagelkerke's $R^2 = 0.058$. APS: Attenuated psychotic symptoms.

Table 35 Combined effects of selected age, sex and symptoms (hallucinatory attenuated psychotic symptoms/brief intermittent psychotic symptoms) predictors on presence of any non-psychotic axis-I disorder

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Sex	-0.515	0.112	21.005	1	0.000	0.598	0.480	0.745
APS	1.099	0.150	53.835	1	0.000	3.002	2.238	4.026

Reference group of sex is females. GoF: $\chi^2(2) = 74.44$; $P < 0.001$; Nagelkerke's $R^2 = 0.046$. APS: Attenuated psychotic symptoms.

Table 36 Combined effects of selected age, sex and symptoms (speech-disorganization attenuated psychotic symptoms) predictors on presence of any non-psychotic axis-I disorder

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Sex	-0.599	0.112	28.561	1	0.000	0.550	0.441	0.685
Age and APS	0.061	0.013	21.201	1	0.000	1.063	1.036	1.091

Reference group of sex is females. GoF: $\chi^2(2) = 45.67$; $P < 0.001$; Nagelkerke's $R^2 = 0.029$. APS: Attenuated psychotic symptoms.

Table 37 Combined effects of selected age, sex and criteria (≥ 1 clinical high risk criterion) predictors on presence of any non-psychotic axis-I disorder

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Sex	-0.525	0.112	21.784	1	0.000	0.592	0.475	0.738
CHR criterion	1.746	0.231	57.300	1	0.000	5.734	3.648	9.012

Reference group of sex is females. GoF: $\chi^2(2) = 77.35$; $P < 0.001$; Nagelkerke's $R^2 = 0.048$. CHR: Clinical high risk.

Table 38 Combined effects of selected age, sex and criteria (≥ 1 European Psychiatric Association criterion) predictors on presence of any non-psychotic axis-I disorder

	Beta	SE	Wald	df	*P* value	Exp (Beta)	95%CI; lower	95%CI; upper
Sex	-0.543	0.112	23.516	1	0.000	0.581	0.466	0.724
EPA criterion	2.066	0.334	38.306	1	0.000	7.896	4.104	15.192

Reference group of sex is females. GoF: $\chi^2(2) = 62.16$; $P < 0.001$; Nagelkerke's $R^2 = 0.039$. EPA: European Psychiatric Association.

ARTICLE HIGHLIGHTS

Research background

Age and sex are crucial aspects in neurodevelopment and are partly interrelated, presenting as important factors in mental disorders related to neurodevelopment. One example of these disorders are psychotic disorders whose age-at-onset and type (affective *vs* non-affective) are influenced by sex. Furthermore, in community samples, clinical high risk (CHR) symptoms and criteria that are currently used for an early detection of psychosis, *i.e.*, attenuated and transient psychotic as well as cognitive and perceptual basic symptoms, were reported to be more frequent and less clinically relevant in children and adolescents in whom CHR criteria are also related to lower rates of conversion to psychosis.

Research motivation

From the differences in these age thresholds, *i.e.*, around age 16 for attenuated psychotic symptoms, and around age 18 and 23 for perceptual and cognitive basic symptoms, it was speculated that sex differences in brain and cognitive maturation might lead to lower age thresholds in the clinical significance of BS and possibly APS in females compared to males. Yet, studies on the interaction of age and sex on CHR symptoms and criteria are lacking.

Research objectives

The main objective was to examine the association of age and sex on the presentation and clinical relevance of clinical high-risk criteria and their constituting symptoms in a large community study of 8- to 40-year-olds.

Research methods

We investigated the effect of both age and sex on the prevalence of CHR criteria and symptoms and on their association with psychosocial impairment and mental disorder in a community sample of $n = 2916$ 8- to 40-year-olds. The sample was composed of community participants in two studies: The "Bern Epidemiology At-Risk" (BEAR) study and the "Binational Evaluation of At-Risk Symptoms in Children and Adolescents" (BEARS-Kid) study. Both studies used a stratified sampling method to obtain a representative sample of 7370 people aged 16–40 years in the BEAR study (response rate: 63.4%) and of 980 minors aged 8-17 years in the BEARS-Kid study (response rate: 32.6%) from citizens of the Swiss Canton of Bern.

Research results

Five hundred forty-two (18.6%) participants reported any CHR symptom; of these, 261 (9.0%) participants reported any one of the 11 criteria relevant cognitive and perceptual basic symptoms, and 381 (13.1%) any one of the five attenuated or transient psychotic symptoms. Fewer participants met any one of the four symptomatic CHR criteria ($n = 82$, 2.8%). Both age and sex were significantly associated with CHR symptoms and criteria, mostly by younger age and female sex. Though slightly differing between symptom groups, age thresholds were detected around the turn from adolescence to adulthood, *i.e.*, around age 18; they were highest for cognitive basic symptoms and CHR criteria, *i.e.*, around age 23. With the exception of the infrequent attenuated psychotic symptom "speech disorganization", the interaction of age with CHR symptoms and criteria predicted functional impairment; whereas, independent of each other, sex and CHR symptoms mostly predicted mental disorders. Only once, in case of functional impairment, an interaction of both age and sex with CHR symptoms – perceptual basic symptoms – became significant.

Research conclusions

Next to confirming the important role of age and sex in the prevalence and clinical relevance of CHR symptoms and criteria, their differential relations to CHR symptoms reveal important insight in possible causal pathways.

Research perspectives

In psychosis research, future efforts at unravelling causal pathways of psychosis, at biomarker discovery and at early therapeutic intervention should consider effects of both sex and age.

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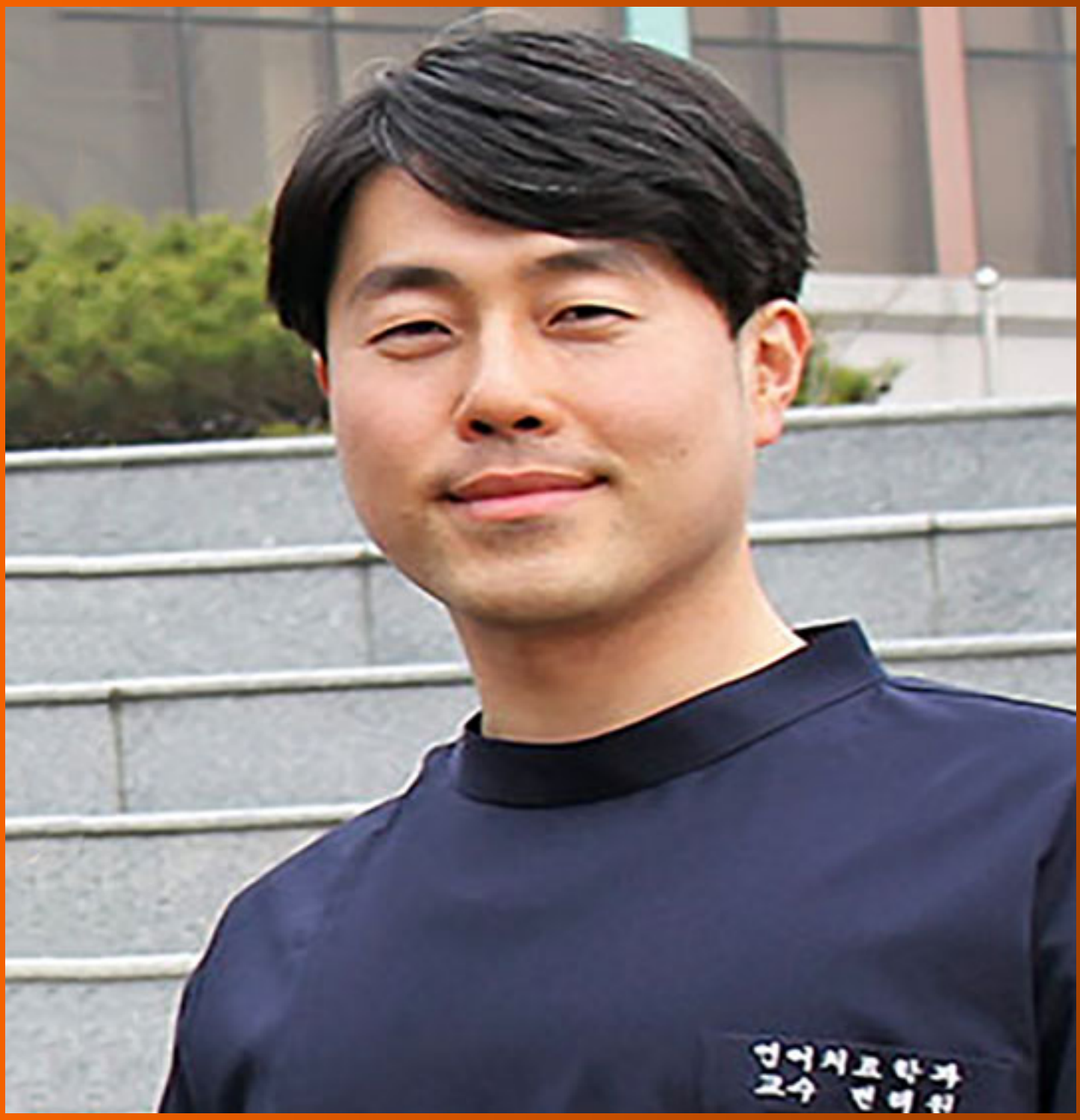


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MINIREVIEWS

Neuropsychiatric issues after stroke: Clinical significance and therapeutic implications

Shuo Zhang, Michael Xu, Zhi-Jun Liu, Juan Feng, Yan Ma

ORCID number: Shuo Zhang (0000-0002-4367-0026); Michael Xu (0000-0002-0248-6097); Zhi-Jun Liu (0000-0001-5533-3038); Juan Feng (0000-0002-1815-7036); Yan Ma (0000-0002-0900-0926).

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Shuo Zhang, Juan Feng, Department of Neurology, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Michael Xu, Department of Clinical Medicine, International Education School, China Medical University, Shenyang 110004, Liaoning Province, China

Zhi-Jun Liu, Yan Ma, Department of Ultrasound, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Corresponding author: Zhi-Jun Liu, MD, PhD, Assistant Professor, Department of Ultrasound, Shengjing Hospital of China Medical University, 36 Sanhao Street Heping District, Shenyang 110004, Liaoning Province, China. liuzj1@sj-hospital.org

Abstract

A spectrum of neuropsychiatric disorders is a common complication from stroke. Neuropsychiatric disorders after stroke have negative effects on functional recovery, increasing the rate of mortality and disability of stroke survivors. Given the vital significance of maintaining physical and mental health in stroke patients, neuropsychiatric issues after stroke have raised concerns by clinicians and researchers. This mini-review focuses on the most common non-cognitive functional neuropsychiatric disorders seen after stroke, including depressive disorders, anxiety disorders, post-traumatic stress disorder, psychosis, and psychotic disorders. For each condition, the clinical performance, epidemiology, identification of the therapeutic implication, and strategies are reviewed and discussed; the main opinions and perspectives presented here are based on the latest controlled studies, meta-analysis, or updated systematic reviews. In the absence of data from controlled studies, consensus recommendations were provided accordingly.

Key words: Stroke; Neuropsychiatric disorders; Depression; Anxiety; Post-traumatic stress disorder; Psychosis

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Core tip: The purpose of this mini-review is to summarize the research advance of neuropsychiatric disorders including depressive disorders after stroke, anxiety disorders after stroke, post-traumatic stress disorder after stroke, post-stroke psychosis, and psychotic disorders. Recent evidence showed that neuropsychiatric disorders after stroke are associated with worsened outcomes yet are still under-recognized. With the exception of depressive disorders after stroke, the other neuropsychiatric disorders lack

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reliable and high-quality evidence in clinical practice. Further studies should attempt to develop protocols or guidelines for the diagnosis, treatment, or prevention of neuropsychiatric disorders after stroke.

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INTRODUCTION

With the aging of the global population, stroke has become the second leading cause of death for people over age 60 and the fifth leading cause in people between the ages of 15 and 59 worldwide. Due to brain damage and loss of function, stroke is also a major cause of long-term disability in adults worldwide, which decreases the quality of life for patients and increases the global medical burden[1]. Recently, neuropsychiatric issues appearing after stroke have raised concerns for clinicians and researchers. Psychiatric disorders are common complications post-stroke and are associated with worsened outcomes, including low quality of life, increase in the burden of caregiving, and unfavorable functional status[2,3]. Even early neuropsychiatric disorders after stroke (NDS) may increase the risk of mortality and recurrence in patients with stroke[4,5]. The current management and treatment of the majority of NDS is not satisfactory, except for some antidepressants that show therapeutic benefit[3,6]. Patients with NDS do not even benefit from existing advanced medical intervention. A retrospective study showed patients with stroke and neuropsychiatric co-morbidities were slightly less likely to receive carotid revascularization intervention compared to those who did not have neuropsychiatric co-morbidities[7]. A lack of subjective intervention willingness from patients and inadequate social and family support may be the reason for the difference in intervention.

Neuropsychiatric impairment after stroke encompasses a wide spectrum of diseases, including neurocognitive disorders and non-cognitive disorders[8]. In this review, we will put an emphasis on discussing the most common non-cognitive NDS after stroke or transient ischemic attacks (TIA): Depressive disorders and anxiety disorders, as well as post-traumatic stress disorder (PTSD), psychosis and psychotic disorders after stroke. Uncommon conditions such as apathy, personality disorders, emotional lability, emotional incontinence, fatigue, mania, catastrophic reactions, and some manifestations of NDS will not be included in this review. These conditions were excluded because these disorders and their manifestations do not have widely acknowledged diagnostic criteria at present, have not established definitions, or are not regarded as standard neuropsychiatric diseases in the fifth edition of the diagnostic and statistical manual of mental disorders (DSM-5)[9]. Something particularly noteworthy is that some patients may suffer from co-occurring NDS (*i.e.*, depression and anxiety) after stroke. Although there exists substantial overlap of symptoms between these NDS, each issue will be reviewed separately.

This review will address the clinical significance for stroke, screening, and identification of each NDS. We then will focus on therapeutic implications and discuss strategies.

The purpose of this mini-review is to outline the current research in the field of NDS, including clinical presentation, epidemiology, therapeutic implications, and strategies to alleviate neuropsychiatric symptoms, to improve the well-being of patients, and to reinforce physical and mental status for stroke survivors. We focused on clinical significance and therapeutic strategies. Our opinions on management and treatment mainly depend on results from studies of evidence-based medicine and expert consensus.

Risk factors for NDS

Genetic background and family history are considered to be important potential susceptibility factors that can affect NDS. A meta-analysis showed that stroke patients with a family history of psychiatric disorders have an increased risk for developing post-stroke depression[10]. Several studies have also identified a number of potential candidate genes that may underlie susceptibility to depressive and anxiety disorders

after stroke. Serotonin transporter gene is the most common gene associated with depression. A meta-analysis of four studies with 641 individuals indicated that there was a positive association between the homozygous short variation allele genotype of the serotonin transporter-linked promoter region (5-HTTLPR) and post-stroke depression, whereas the homozygous long variation allele genotype of 5-HTTLPR showed a significant negative association with post-stroke depression. The heterozygous short and long allele genotypes for 5-HTTLPR or rs25531 and *STin2 VNTR* gene polymorphisms of the serotonin transporter gene have not been proven to be susceptibility genes for post-stroke depression[11]. Although the 5-HTTLPR polymorphism was found to have a significant association with an antidepressant response and remission in Caucasians[12], the relationship between the 5-HTTLPR polymorphism and the responsiveness of antidepressants for post-stroke depression remained not well-determined.

It was reported that stroke patients with brain-derived neurotrophic factor gene hypermethylation levels and brain-derived neurotrophic factor gene polymorphisms had a higher risk of developing post-stroke depression and post-stroke anxiety (PSA)[13,14]. In addition, polymorphism in the tryptophan hydroxylase 2 gene were also found to be involved in PSA susceptibility[15].

NDS is multifactorial and influenced by many other demographic and external factors. A meta-analysis published in 2017 with 36 studies analyzed the research status and emerging trends in regard to risk factors for post-stroke depression, and suggested that the correlation between a history of psychiatric disorders and post-stroke depression was highest among all factors; other demographic and external risk factors for post-stroke depression were female, age (< 70 years), stroke severity, functional impairments, and lack of social and family support[16]. However, one other meta-analysis also published in 2017 with 18 studies concluded that gender, age, and social factors were not reliable risk factors[17]. Moreover, a recent study confirmed that unmarried status and excessive fatigue were potential negative risk factors for PSA[18].

Medical conditions and socioeconomic status, such as time to access of health services, willingness to seek treatment, health insurance coverage, medical expenditure, and educational level may have a partial effect on NDS[19,20]. However,few prospective studies have focused on the above factors for the development and evolution of NDS. Features of neuropsychiatric disorders after stroke is shown in Table 1.

DEPRESSIVE DISORDERS AFTER STROKE

Screening and identification

Post-stroke depressive (PSD) disorders are the most commonly reported and widely investigated among all types of NDP in the literature. PSD is the most frequent treatable neuropsychiatric complication of stroke at any one time after onset. A prospective study showed PSD can occur from 1 to 18 mo after the onset of stroke, and prevalence of PSD was not found to vary considerably over time (the prevalence at 1, 3, 6, 12, and 18 mo were 24.5%, 27.1%, 28.3%, 19.8%, and 26.3% respectively)[21].

A previous meta-analysis of 61 studies with 25488 patients indicated that the pooled frequency of PSD was 34% in 32 stroke cohorts[22], consistent with a meta-analysis of 32 studies with 8938 patients receiving antidepressant therapy where the pooled frequency was 31%[23].

The proportional frequency of depression reported ranged from 5%[24]-84%[25], which varied considerably across studies because of different PSD identification criteria, threshold time points of assessment during follow-up, and clinical setting. A national register-based cohort study in Denmark consecutively recruited 157243 first-time hospitalized patients with new-onset PSD and 160236 local healthy residents as a reference population during 2 years of follow-up between 2001 and 2011. The total incidence of depressive disorders after stroke was 25.4%, compared with 7.8% in the control population[26].

Compared with orthopedic patients with similar degrees of motor disability[27], myocardial infarction, and similar predisposing factors of cardiovascular disease[23], patients with stroke are more likely to suffer from depressive disorders, suggesting that there is a more complex neurobiological mechanism for the etiology of PSD.

Generally, PSD occurs in the range from 25%-35% of stroke survivors with the frequency estimated to be the highest in the 1st year after onset, with gradually declining prevalence thereafter[28].

Optimal screening for and identification of PSD is vital for following treatment and management; however, there is currently no established diagnostic criterion for PSD. The DSM-5 classifies PSD as a "depressive disorder due to another medical

Table 1 Features of neuropsychiatric disorders after stroke

Disorders	Prevalence/ frequency, %	Main clinical manifestations	Screening tools	Identification	Management and treatment
Depressive disorders after stroke	5-84	Depressed mood; marked reduction in interest or pleasure in activities; decreased/increased appetite/weight; insomnia or hypersomnia; psychomotor agitation/retardation; loss of energy/fatigue; feelings of worthlessness/inappropriate guilt; loss of concentration; appear pessimistic about health issues/recurrent thoughts of death or suicide	Center for epidemiological studies-depression scale; hospital anxiety depression scale; Hamilton depression rating scale; beck depression inventory; geriatric depression scale; PHQ-9	According to the DSM-5 classification, PSD is defined as a depressive disorder due to TIA or stroke.	SSRIs and SNRIs; psychological intervention; mental and physical exercise; neuromodulation
Anxiety disorders after stroke	20-24	Prominent anxiety; excessive fear, worry, and concern about health issues; intense dread or uneasiness; panic attacks, or obsessions or compulsions predominate	Hamilton anxiety scale; hospital anxiety and depression scale-anxiety subscale	According to the DSM-5 classification, PSA is defined as an anxiety disorder due to TIA or stroke.	SSRIs; Tricyclic antidepressant; benzodiazepines; "Z-drugs" (zolpidem, zaleplon and eszopiclone); psychological interventions; mind-body interventions
PTSD after stroke	8.3-29.6	Intrusive memories; alterations in physical reactions and arousal; avoidance; negative alterations in cognition and mood	PTSD checklist for a stressor, TIA or stroke as stressor; clinician administered PTSD scale; impact of events scale-revised; posttraumatic stress diagnostic scale; structured clinical interview for DSM	PTSD is related to TIA or stroke which creates psychological trauma in response to actual or threatened death, serious injury, and adverse life events.	Psychotherapeutic approach procedures; antidepressants, anxiolytics sympathetic inhibitor, antipsychotics, anticonvulsants, and sedative drugs
Psychosis and psychotic disorders after stroke	4.67-5.05	Hallucinations or delusions; disorganized speech; catatonic or inappropriate motor behavior	Neuropsychiatric inventory	According to the DSM-5 classification post-stroke psychotic disorders are defined as psychotic disorders due to TIA or stroke.	Antipsychotic drugs; neuromodulation and psychosocial therapy; psychological intervention

TIA: Transient ischemic attacks; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin-norepinephrine reuptake inhibitors; PSD: Post-stroke depressive; PSA: Post-stroke anxiety; PTSD: Post-traumatic stress disorder; PHQ-9: 9-item patient health questionnaire; DSM-5: Diagnostic and statistical manual of mental disorders.

condition". The identification and diagnosis of PSD is usually based on the combination of detailed clinical assessment and screening scale tools in the clinical practice. For example, clinicians diagnose PSD using a structured clinical interview for DSM-5 combined with a screening scale before initiating PSD treatment. There is no universally accepted screening tool for PSD. The following psychiatric scales are frequently used to measure PSD symptoms in clinical study and practice: The center for epidemiological studies depression scale, hospital anxiety depression scale, Hamilton depression rating scale, beck depression inventory, geriatric depression scale, and nine-item patient health questionnaire (PHQ-9). In 2017, the American Heart Association and American Stroke Association jointly issued the first scientific consensus statement for healthcare, which comprehensively discussed the epidemiology, pathophysiology, screening, management, and prevention of PSD[28]. Based on the results of a meta-analysis with 2907 participants, the center for epidemiological studies depression scale, Hamilton depression rating scale, and PHQ-9 scores have proven to have higher sensitivities for identifying PSD, using the international classification of disease or DSM diagnosis of depression as the reference standard[29]. The PHQ-9 is one of the most commonly used tools for screening for PSD with high validity and reliability in primary care. One individual patient's data meta-

analysis showed that a cutoff of a score of 10 on the PHQ-9 yielded a maximum diagnostic performance[30]. Considering the structured interview for DSM as the reference standard for PSD, the sensitivity and specificity of PHQ-9 were 0.82 and 0.97, respectively. The overall diagnostic performance of the PHQ-9 was better than the hospital anxiety depression scale-D and geriatric depression scale[31]. Another individual participant's data meta-analysis of PHQ-9 reported the existence of selective cutoff reporting bias when estimating sensitivity in most studies[32]. In addition, a systematic review concluded that the results regarding the sensitivity and specificity of the PHQ-9 for PSD screening and identification were uncertain[33].

Remarkably, unlike depressive disorders caused by other diseases, screening for PSD faces many challenges; particular attention should be paid to the actual condition of patients with stroke. Neurological symptoms resulting from stroke such as aphasia, alexia, or agnosia may lead to expressive or receptive dysfunction[34]. Cognitive impairment such as loss of concern, anosognosia, abulia, or lack of insight may develop similar depressive symptoms[35]. The above adverse factors for screening could hinder the identification and diagnosis of PSD. Therefore, screening and identification procedures of PSD should be performed following protocols tailored to the individual.

Management and therapeutic implication

PSD is associated with worsened functional outcomes after stroke. A meta-analysis including 14 studies before May 2018 with 17609 PSD patients evaluating the association between PSD and the mortality of different follow-up times revealed that PSD showed a negative impact on survival rates; the effect of PSD on short-term mortality was slightly higher than its effect on long-term mortality[4]. A recent case-control study showed PSD increased disability severity in ischemic stroke survivors, whose Barthel index and Rivermead mobility index scores were both lower than stroke survivors without PSD at both admission and discharge[36].

In theory, the early and prophylactic use of PSD may reduce the risk of PSD in stroke survivors. A meta-analysis with eight prospective randomized controlled trials published from 1990 to 2011 revealed that antidepressant prophylaxis (mianserin, fluoxetine, nortriptyline, sertraline, escitalopram, milnacipran) reduced the odds of developing PSD, and pooled results uncovered the benefit of early initiation of pharmacotherapy in stroke patients[37]; however, the final conclusion of this review was based on eight studies with four classes of antidepressants [selective serotonin reuptake inhibitor (SSRI), tetracyclic antidepressant, tricyclic antidepressant, serotonin-norepinephrine reuptake inhibitor (SNRI)]. Therefore, there may be a high relative heterogeneity among the studies. A systematic review just published in November 2019, which retrieved data from 2009 to 2018, suggested that the use of SSRIs, psychological intervention [*e.g.*, cognitive behavioral therapy (CBT)], as well as mental and physical exercise could relieve most mood symptoms of PSD, but the level of evidence quality of the included studies were low to moderate[38]. A meta-analysis including 20 studies with 1485 patients indicated that both SSRIs and SNRIs had favorable therapeutic effects on PSD, and furthermore that citalopram may improve depressed moods faster than other SSRIs[39].

Fluoxetine for motor recovery after acute ischemic stroke is a randomized placebo-controlled trial conducted in France, which included 118 patients with ischemic stroke and moderate-to-severe motor deficits, found that the early use of fluoxetine with physiotherapy promoted motor recovery after 3 mo[40]. Similar to the conclusion of fluoxetine for motor recovery after acute ischemic stroke, most meta-analyses and systematic reviews published before 2019 supported that, if given early, fluoxetine could alleviate neurological deficits and disability and allow patients to recover independently through rehabilitation after stroke[41-43].

With the release in December 2018 of results on the effect of fluoxetine on functional outcomes after acute stroke (FOCUS), SSRI-modulated neuroplasticity that could enhance neurological recovery began to be questioned. The FOCUS trial is a multicenter randomized double blind and parallel control, collaborative study held at 103 hospitals through the National Health Service, United Kingdom, which focuses on the effect of fluoxetine on neurological functional outcomes after acute stroke.

In FOCUS, from 2 to 15 d after onset, there were 3,127 eligible patients with stroke (not patients with PSD) that were recruited and randomly allocated fluoxetine (20 mg daily) or placebo for 6 mo. After an extended follow-up period of up to 12 mo, only the neuropsychological scale questionnaire showed statistically significant differences between the two groups, although results of the clinical trial indicated that fluoxetine would enable the improvement of depression symptoms rather than clinical outcomes, and even increase the risk of bone fractures. The results from the FOCUS trial do not support the routine use of fluoxetine in prophylactic treatment for PSD or to promote the recovery of neurological function[44]. The TALOS study (the Efficacy of

Citalopram Treatment in Acute Stroke) was a placebo-controlled, randomized, double-blind study with 642 stroke patients in Denmark. Similarly to the FOCUS results, the TALOS study also did not show that citalopram could promote functional recovery, reduce the dependence on activities of daily living, or decrease the risk of recurrent cardiovascular events in acute ischemic stroke[45].

Since the FOCUS study has the largest number of patients among similar studies so far, the results from the FOCUS study undoubtedly carry a higher weight in the present meta-analysis. Both a recent systematic review[46] and a meta-analysis[47] that encompassed FOCUS data did not support the routine prescription of fluoxetine or other SSRIs to reduce and promote function recovery early after stroke without PSD. Instead, they suggested that fluoxetine or other SSRIs might be used to treat depressive disorders in patients with PSD. Nonetheless, the present result may not be the final conclusion, and the therapeutic effect of SSRIs and SNRIs for PSD functional rehabilitation remains controversial. Consequently, the two big ongoing trials, assessment of Fluoxetine in Stroke recovery (participants are being recruited from Australia, New Zealand and Vietnam), and efficacy of fluoxetine, a randomized Controlled Trial in Stroke (participants are being recruited from Sweden) will provide further information regarding fluoxetine for stroke recovery[48]. In addition, a meta-analysis using individual participant data will be needed[47].

SSRIs and antithrombotics are always simultaneously prescribed for patients with PSD in clinical practice. Clopidogrel is one of the commonly used anti-platelet medications that prevent and treat ischemic stroke. Clopidogrel can be metabolized into active products with therapeutic properties by cytochrome P450 (CYP) enzymes. A cohort study and meta-analysis (which included 72020 participants) have shown that CYP2C19-inhibiting SSRIs (fluoxetine and fluvoxamine) can decrease the therapeutic efficacy of clopidogrel. Patients using clopidogrel who were co-prescribed CYP2C19-inhibiting SSRIs had an 11% higher risk of developing ischemic disease than patients using clopidogrel who were treated with non-inhibiting SSRIs[49]. Serotonin could be released from platelets in the blood during the coagulation process. Aspirin is another important prescription medication for treating and preventing ischemic stroke and TIA. In theory, SSRI and SNRI reuptake serotonin in platelets as well as they do in the central nervous system, which reduce platelet serotonin and may be associated with aspirin-related bleeding[50].

Therefore, there are also growing concerns on the relationship of SSRIs with abnormal bleeding events[51]. Mortensen's study demonstrated that prestroke SSRI exposure was significantly associated among the severity and mortality of patients with hemorrhagic stroke[52]. In a large collaborative study, the preadmission use of SSRI alone did not increase the risk of spontaneous intracerebral hemorrhage after intravenous thrombolytic therapy for acute ischemic stroke. While there was a significant interaction between the concurrent preadmission use of SSRIs and oral anticoagulants on the occurrence of intracerebral hemorrhage related to thrombolysis[53], this condition can be seen in PSD patients with recurrent acute ischemic stroke that are treated with SSRIs. Moreover, fluoxetine and fluvoxamine are reported to have potential interactions with warfarin, and inhibit warfarin metabolism by competitively binding plasma protein and interfering with CYP isoenzymes, which are more likely to strengthen the anticoagulant effects of warfarin. Paroxetine also seems to have a low-to-moderate risk of enhancing the pharmacological effects of warfarin; however, other SSRIs and SNRIs do not appear to interact with warfarin[54].

A recent systematic review suggested that there is no high quality evidence to support that SSRIs used alone can increase the risk of spontaneous intracerebral hemorrhage. In addition, the association between SSRIs and intracerebral hemorrhage as previously reported was partly accounted for by biases and methodological limitations[55]. Neurologists and psychiatrists need to be well aware of the pharmacological interaction profiles when co-prescribing antidepressants and antithrombotics to patients with PSD and other NDS, monitor the possible adverse events during follow-up, and provide tailored therapeutic strategies for treating PSD and other NDS.

Psychotherapy is also an important intervention for PSD. CBT may be the most effective psychotherapeutic intervention. A meta-analysis on the efficacy of psychotherapy for PSD concluded that the evidence for the benefit of CBT in PSD remains inconclusive due to the high degree of heterogeneity and low quality across the majority of included studies[56]. Neuromodulation, such as transcranial magnetic stimulation and transcranial direct current stimulation, are promising adjunctive therapies. However, high quality randomized controlled trials using psychotherapy or neuromodulation are limited, and further research is needed[57].

In summary, antidepressant therapy should be used early once the definitive diagnosis of PSD has been made. SSRIs and SNRIs are recommended as a first-line

pharmacotherapy for mitigating depression. Other treatment approaches, *i.e.*, psychotherapy, neuromodulation, and psychosocial interventions, should also be considered. No reliable evidence exists to show that the use of SSRIs and other antidepressants can improve neurological function outcomes for patients with PSD.

ANXIETY DISORDERS AFTER STROKE

Screening and identification

PSA disorders are relatively common psychological problems and are the secondary NDS after depressive disorders. There are several distinct types of anxiety disorders: generalized anxiety disorder, phobias, selective mutism, agoraphobia, social anxiety disorder, and panic disorders. These disorders share similar core psychological symptoms, including feelings of uneasiness, excessive and persistent worry, and fear. Notably, anxiety disorders can also be accompanied by significant physical symptoms, some of which resemble neurological manifestations, such as tense muscles, dizziness, numb or tingling hands or feet, headache, chronic muscle or joint pain, and disturbed sleep[58]. Furthermore, unfavorable physical conditions due to brain damage caused by stroke, such as chronic pain, sleep disturbance, and communication difficulties, posed a high risk of developing PSA[59].

A case-control study conducted in Sweden revealed that the odds of PSA were predominantly higher than in the control population, which cannot be attributed to higher rates of comorbid depression. Remarkably, PSD did not show a significant independent association with PSA[60]. A meta-analysis reported that the frequency of PSA gradually rises over time, which ranged from 20% [95% confidence interval (CI): 13%-27%] within 1 mo, 23% (95%CI: 19%-27%) for one to five-mo after stroke, to 24% (95%CI: 19%-29%) for 6 mo or more after stroke[61]. The DSM-5 classifies PSA as an "anxiety disorder due to another medical condition". The prognosis of patients with PSA was markedly poor, as they likely suffered from persistent dependence with poorer quality of life and restricted social participation at 3 mo after stroke[62]. Similarity, a longitudinal study in South Korea found that PSA occurs within 2 wk after stroke, which may be an independent detrimental factor for long-term functional outcomes and daily life activities[63].

The Hamilton anxiety scale and the hospital anxiety and depression scale-anxiety subscale are the most commonly used to screen and measure the anxiety symptom severity of PSA. The cutoff score of possible and probable diagnosis of hospital anxiety and depression scale-anxiety subscale was the most widely considered identification criterion[59].

Management and therapeutic implication

There are no widely accepted guidelines that have been developed for the treatment of PSA. Several classes of pharmacotherapy were used to treat PSA in clinical practice, including SSRIs, tricyclic antidepressants, benzodiazepines and "Z-drugs"[64]. Likewise, various forms of psychological interventions, such as CBT, were frequently used for PSA, but few high-quality intervention studies have been shown.

In a study by Chun *et al*[62,64,65], meta-analysis including four pharmacotherapy comparisons studies (three studies published in Chinese journals) using paroxetine, imipramine, and buspirone, as well as eight psychotherapy comparisons studies showed an overall favorable pharmacotherapy and psychotherapy effect compared with control; however, the heterogeneity of the included studies of this meta-analysis was high and the quality of literature was relatively low. The positive conclusion may be driven by risk of bias[65]. In line with the study by Chun *et al*[64], a Cochrane review suggested that there was no high-quality clinical evidence to guide PSA management. Large-scale randomized double-blind controlled trials are required to determine the efficacy of pharmaceuticals and psychological therapies[64].

A systematic review revealed that mind-body interventions (*i.e.*, yoga, Tai Chi) may have potential benefits for treating both PSA and PSD by improving the mood and quality of life of stroke survivors[66]. Likewise, self-help mindfulness and relaxation techniques have been reported to be effective self-administered therapies to help alleviate symptoms, especially for patients with communication difficulties[67]. This suggests that PSA subtypes[62] and tailored therapeutic strategies are vital for future interventional studies.

PTSD AFTER STROKE

Screening and identification

PTSD is a mental health condition that develops following a traumatic event, including acute stroke and TIA. Under the DSM-5, PTSD is categorized as a subtype of anxiety disorder. The occurrence of PTSD is related to an event that creates psychological trauma in response to actual or threatened death, serious injury, and adverse life events. PTSD has four main hallmark characteristics: (1) Intrusive memories; (2) Alterations in physical reactions and arousal; (3) Avoidance; and (4) Negative alterations in cognition and mood[68]. As an unexpected "traumatic" event, acute stroke or TIA may be considered to be potentially life-threatening or as severe disability disorders by patients. A growing body of clinical evidence has highlighted PTSD as a common result of neuropsychiatric sequelae of stroke or TIA[69].

Patients with post-stroke PTSD were likely to combine PSD and PSA[70]. A cross-sectional study showed that PSD, PSA, and post-stoke PTSD have a remarkably high degree of co-occurrence (approximately 40% patients with NDS comorbidity have the above three psychiatric disorders)[2]. However, the biological mechanism and clinical significance of overlap and comorbidity among these NDSs have yet to be well elucidated[68]. Studies report that the frequency of poststroke PTSD was varied, which depended on the type of stroke, assessment time-point, and morbidity condition[71,72]. Notably, the incidence rate was even as high as 37% in survivors with spontaneous subarachnoid hemorrhage, which was disadvantageous to patient quality of life and outcome[73]. A retrospective study with 12 mo follow-up showed that the prevalence of probable PTSD was lower within 1-year than that within 3 mo (8.3% compared with 29.6%) after TIA, suggesting that the risk of PTSD declined gradually over time after onset, This improvement could be due to the reversibility and transience of TIA, and the trauma event and psychological distress might therefore be more likely to be temporary unless it progresses into ischemic stroke[74]. A meta-analysis with data collected before January 2013 also suggested that the prevalence of PTSD after stroke and TIA was 23% within 1 year of onset and 11% after 1 year[75]. PTSD after stroke might have a worse effect on the mental health of survivors and an undesirable functional prognosis[76]. Correspondingly, patients with PTSD also had a higher risk of developing stroke than control people without PTSD[77]. A similar association was also seen in veterans with PTSD[78], but whether PTSD treatment offset the risk of developing stroke or TIA is unknown. Additionally, the treatment adherence to medication prescribed by specialists of stroke or TIA survivors with PTSD was reported to be poor[79], which impeded the efficient management of mental and physical health.

In most studies, PTSD after stroke was identified by the combination of diagnostic interviews and self-rating scales and questionnaires. A variety of assessments was used for screening; more frequently used scales included the PTSD checklist for a stressor using the "stroke or TIA" as a stressor[71,76,79], the clinician-administered PTSD scale[80], impact of events scale-revised[72], posttraumatic stress diagnostic scale[70], as well as the structured clinical interview for DSM. As the most widely used scale at present, a cutoff score of 50 on the PTSD checklist for a stressor highly indicated probable PTSD diagnosis after stroke.

Management and therapeutic implications

To our knowledge, there is no high-quality randomized controlled trial evaluating the efficacy of pharmacotherapy or psychotherapy for the intervention of post-stroke PTSD[68,69]. The psychotherapeutic approach procedures, such as CBT, trauma-focused psychotherapies, and exposure therapy are useful for facilitating compliance for developing strategies, which look promising for post-stroke PTSD of which the efficacy needs to be tested in future studies[81]. It remains unclear whether post-stroke PTSD could benefit from pharmacotherapeutic interventions like PSD, such as SSRI antidepressants. Although antidepressants were usually administrated for patients with post-stroke PTSD with comorbid depressive disorders, evidence for the effectiveness of medication (antidepressants, anxiolytics sympathetic inhibitor, antipsychotics, anticonvulsants, and sedative drugs) has still been inconsistent[82].

PSYCHOSIS AND PSYCHOTIC DISORDERS AFTER STROKE

Screening and identification

Under DSM-5 classifications, post-stroke psychotic disorders may be categorized as psychotic disorders due to another medical condition. The main symptoms of post-stroke psychotic disorders are characterized by hallucinations or delusions, which may be accompanied by disorganized speech, catatonic or inappropriate motor behavior, typically followed by acute severe stroke. Post-stroke psychosis refers to a series of symptoms after stroke; psychosis can be a clinical syndrome embedded with

many medical conditions, including schizophrenia, bipolar disorder with psychotic properties, and other psychotic disorders. The most prominent symptoms of psychosis include delusions and hallucinations[83]. Psychosis may manifest within 1 wk after stroke and rapidly develop into psychotic disorders, but psychosis would also be delayed and occur several weeks after onset. Delusions and hallucinations may be permanent as an accompanying sequel, or temporary as a result of functional rehabilitation.

Post-stroke psychosis didn't appear to notably raise many clinical research concerns like PSD or PSA, resulting in the lack of robust consensus supported by evidence-based medicine. Previous studies have suggested that post-stroke psychotic disorders are a rare complication of stroke. A cohort study published in 1991 included 1191 stroke patients with a 9-year follow-up, of whom only five patients were identified to suffer psychosis[84]. Although single psychotic symptoms (psychosis) may not meet the criteria of strict psychotic disorders, delusions and hallucinations seem to be more frequent in stroke survivors. A recent meta-analysis reported that the estimated frequency from the eligible four studies with delusions symptom was 4.67%, and the estimated frequency from the three studies with hallucination symptoms was 5.05%, with a pooled prevalence rate of psychosis after stroke of 4.86%[85]. A retrospective study consecutively included 1,108 stroke survivors in Western Australia from 1990 to 2002, and reported the cumulative incidence of psychosis after stroke to be 6.7%, which is a significantly positive correlation with a 10-year mortality[86]. Structural lesions that were related to delusions were centered on the right frontal, temporal, and parietal lobes, as well as white matter lesions with connectivity to the above areas, in addition to the right caudate nucleus[87,88].

Although different versions of the neuropsychiatric inventory were administered to stroke survivors for detecting delusions and hallucinations in some studies[89-91], unfortunately neuropsychiatric assessment tools for psychosis and psychotic disorders after stroke were presented inconsistently in the current studies. Moreover, there is no structured assessment that is suitable for a quantitative evaluation of psychosis and psychotic disorders respectively. It is thus a challenge to represent standardization studies across different research endeavors about psychosis and psychotic disorders after stroke.

There is no widely acknowledged diagnostic criterion for psychosis and psychotic disorders after stroke, and most studies adopt the DSM and International Classification of Diseases as diagnostic criteria for psychotic disorders. Therefore, it is hard to yield consistent conclusions, or to stand in agreement with these promising study results. Such deficiencies have already been highlighted by the latest systematic reviews or meta-analyses on post-stroke psychosis[85,92]. Validated structured assessment tools of psychosis and acknowledged diagnostic criteria are needed to identify the presentation and estimate the severity of psychosis and psychotic disorders after stroke, which will facilitate the standardization of research in this field.

Management and therapeutic implication

Currently, there is no randomized controlled trial study that systematically investigates the therapeutic efficacy and safety of antipsychotic medication for post-stroke psychosis. Most studies applied the management and treatment for post-stroke psychosis in a similar manner with that used for primary psychotic disorders, indicating that they share the same clinical and etiology properties. In some case reports and case series studies, stroke survivors with psychosis or psychotic disorders were mostly treated with antipsychotic medications. Approximately two thirds of patients who were treated with antipsychotics attained complete or partial recovery[85].

Second-generation antipsychotic drugs, such as risperidone, quetiapine, and olanzapine, were the most commonly used antipsychotic medications for post-stroke psychoses. The safety of antipsychotics for patients with stroke is still highly controversial. Antipsychotic drugs appear to have undesirable side effects on glucose and lipid metabolism. Whereas different antipsychotics exhibited distinctly varying degrees of influence on metabolic side-effects, a meta-analysis suggested that olanzapine and clozapine showed the most unfavorable effects on metabolism[93]. Previous studies have concluded that either first or second generation antipsychotic drugs may increase the risk of stroke, especially for patients with vascular dementia[94,95]. A recent meta-analysis revealed that antipsychotic drug exposure may significantly increase the risk of developing a stroke, but the conclusion remains unproven due to the high heterogeneity of these included studies[96]. A meta-analysis indicated that the risk of developing stroke might be higher in patients who received first-generation antipsychotic drugs than in those who received second-generation antipsychotic drugs[97]. However, a large-scale case control study found that neither first nor second generation antipsychotic drugs increase the risk of stroke in elderly

subjects with non-cognitive decline[98]. Therefore, as an important complementary therapy, non-pharmaceutical approaches such as physical neuromodulation and psychosocial therapy are promising therapeutic options for psychosis and psychotic disorders after stroke. It has been shown that CBT might help mitigate the distress caused by hallucinations or delusional beliefs[99].

CONCLUSION

At present, more and more attention is paid to the screening, diagnosis, and management of NDS. There is still lack of a widely-acknowledged structured scale for screening and assessing each NDS. Pharmacotherapy by modulating neurotransmitters is the mainstay treatment modality for NDS. Except for PSD being studied extensively, large-scale randomized double-blind controlled trials are still required to determine the efficacy of pharmaceuticals and psychological therapies for other NDS. Further aim should attempt to develop protocols or guidelines for the diagnosis, treatment, or prevention of NSD. Current evidence reveals the limitations of our knowledge about NDS and may change as scientific research reflects that stroke is the pathological basis and cause of NDS.

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ORIGINAL ARTICLE

Observational Study

Visual impairment and depression: Age-specific prevalence, associations with vision loss, and relation to life satisfaction

Audun Brunes, Trond Heir

ORCID number: Audun Brunes (0000-0002-0806-5963); Trond Heir (0000-0001-9616-0145).

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Audun Brunes, Trond Heir, Section for Trauma, Catastrophes and Forced Migration - Adults and Elderly, Norwegian Centre for Violence and Traumatic Stress Studies, Oslo NO-0484, Norway

Trond Heir, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, NO-0315, Norway

Corresponding author: Audun Brunes, PhD, Research Scientist, Section for Trauma, Catastrophes and Forced Migration - Adults and Elderly, Norwegian Centre for Violence and Traumatic Stress Studies, PB 181 Nydalen, Oslo NO-0409, Norway. audun.brunes@nkvts.no

Abstract

BACKGROUND

To our knowledge, no study has obtained specific estimates of depression for young and middle-aged adults with visual impairment (VI). As estimates of depression varies across age groups in the general population, it is of interest to examine whether the same applies to adults with low vision or blindness.

AIM

To estimate depression prevalence and its association with VI-related characteristics and life satisfaction in adults with VI.

METHODS

A telephone-based cross-sectional survey was conducted between January and May 2017 in an age-stratified sample of adults who were members of the Norwegian Association of the Blind and Partially Sighted. Participants were asked questions about their sociodemographic characteristics, VI characteristics, and life satisfaction. Depression was measured with the Patient Health Questionnaire. The diagnostic scoring algorithm was used to calculate the point prevalence of depression (*i.e.*, major depression and other depressive disorders) across categories of gender and age (years: 18-35, 36-50, 51-65, ≥ 66). The associations were estimated using regression models.

RESULTS

Overall, 736 adults participated in the study (response rate: 61%). The prevalence estimates of depression varied across different age groups, ranging from 11.1%-22.8% in women and 9.4%-16.5% in men, with the highest rates for the two youngest age groups. Results from the multivariable models including sociodemographic and VI-related variables showed that losing vision late in life [Prevalence ratio (PR), 1.76, 95%CI: 1.11, 2.79] and having other impairments (PR:

given by each participant, the data are to be stored properly and in line with EU Regulation 2017/679 (General Data Protection Regulation (GDPR)). However, anonymized data is available to researchers who provide a methodologically sound proposal in accordance with the informed consent of the participants. Interested researchers can contact project leader Trond Heir (trond.heir@medisin.uio.no) with a request for our study data.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised in accordance with the STROBE Statement-checklist of items.

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1.88, 95%CI: 1.32, 2.67) were associated with higher rates of depression, whereas older age was associated with lower rates (PR: 0.83, 95%CI: 0.74, 0.93). Additionally, participants who were depressed had lower life satisfaction than those who were not depressed (adjusted β: -2.36, 95%CI: -2.75, -1.98).

CONCLUSION
Our findings suggest that depression in adults with VI, and especially among young and middle-aged adults, warrants greater attention by user organisations, clinicians, and healthcare authorities.

Key words: Blindness; Depression; Life satisfaction; Major depression; Vision loss; Visual impairment

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Core tip: Depression in people with visual impairment (VI) goes often unrecognized and untreated, yet knowledge about its occurrence can help to inform the design of mental health services targeting the specific population. The study's findings of a high rate of depressive disorders in adults with VI, particularly among young and middle-aged adults, should in part be interpreted in the light of the extensive stigma, discrimination, isolation, and loneliness that they experience. For depressed adults with VI, the consequences may be severe in terms of a lower quality of life.

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INTRODUCTION

Visual impairment (VI) refers to a substantial and often irreversible loss in one of the functions of the visual system[1]. About 1.3 billion people are classified with near or distance VI on a global basis[2,3] and the numbers are projected to increase in the future due to an aging population and the greater burden of vision-threatening conditions such as diabetes and stroke[2]. Researchers, clinicians and others often refer to VI as a single entity, but VI is, in fact, a highly heterogeneous condition in terms of the visual function affected, onset age, severity, cause, and prognosis of vision loss. A distinction is often made between congenital and acquired vision loss, and between moderate VI, severe VI and blindness[1].

The literature on depression in people with VI is quite extensive[4-12], with many studies suggesting a link between vision loss and depression[6-8,10,12]. However, the prevalence estimates for depression have been found to vary greatly across studies. A meta-analysis of depression or depressive symptoms in people with vision-related conditions revealed that the prevalence estimates ranged between 5% and 57%, with a mean of 25%[12]. Much of the variation in the reported prevalence estimates is related to the inclusion of small and non-representative samples. In addition, most of the studies have been restricted to specific vision conditions or to older adults. Of studies involving young and middle-aged adults from the VI population[8,11], none have estimated the prevalence of depression for these age groups. As estimates of depression differ across different age groups in the general population[13,14], it is of interest to examine whether the same applies to adults with low vision or blindness.

Most studies of people with VI have relied on symptom rating scales in their screening for depression, while few studies have estimated the prevalence of depressive disorders[12,15,16]. Although clinical interviews are considered the gold standard for diagnostic classification, the impracticability of interviews in large surveys has led to the development of brief screening tools that match the criteria set in official diagnostic systems. One such questionnaire is the nine-item Patient Health Questionnaire (PHQ-9)[17]. The PHQ-9 has been applied in research on people with various health conditions[18]. Furthermore, the operational characteristics of the PHQ-9 are either equal or superior to other depression measures[18], and the results of a recent

meta-analysis, which included 40 studies, have confirmed its validity as a diagnostic measure in primary care settings (sensitivity: 41%-71%; specificity: 88%-97%)[19].

There is little consensus in the literature about whether there are certain subgroups of the VI population at greater risk of developing depression than others. Earlier research has mostly focused on the association between the severity of vision loss and depression[4,7,9,11,16,20-22], often finding no relationships[4,5,7,11,20-22], whereas more inconsistent evidence has been reported for factors such as the duration and cause of vision loss[4,9,22]. Furthermore, we have not identified any publications related to the risk of depression among adults with congenital or childhood vision loss, and more research is therefore needed.

We conducted a cross-sectional study that included a large, age-stratified sample of Norwegian adults with VI. Data were obtained *via* structured telephone interviews, and the PHQ-9 was used to obtain a probable diagnosis of current depression. This study had three main aims: To estimate the point prevalence of depressive disorders in stratified age groups of adults with VI; to examine whether depression was associated with different characteristics of vision loss; and to describe the association between depression and life satisfaction.

MATERIALS AND METHODS

Ethical considerations

The Regional Committee for Medical and Health Research Ethics was sought, and the committee confirmed that the study required no formal ethical approval as it was carried out in accordance with principles of anonymized data (Reference number: 2016/1615A). Prior to the survey, the participants were informed about all aspects of the research project, including potential risks and the voluntary nature of the survey. The participants consented by completing the interviews. No identifying information was collected.

Design and participants

An anonymous cross-sectional survey was conducted in an age-stratified sample of adult members (aged ≥ 18 years) of the Norwegian Association of the Blind and Partially Sighted. For a person to be granted full membership of the organization, he or she needs to enclose in their application form medical documentation of either VI or an untreatable eye condition that will progress towards low vision or blindness. Data were collected between January and May 2017, through structured telephone interviews. The interview guide contained more than 120 questions covering a wide range of topics, including sociodemographic factors, cause and onset of vision loss, serious life events, coping, mental health, and quality of life. Each interview took about 30 min to complete.

Most people with VI are of old age[1]. We therefore used an age-stratified sampling technique to allow for more precise estimations across all age groups in the adult VI population. First, the study population was divided into four age groups (years: 18-35, 36-50, 51-65, ≥ 66) and then we surveyed an equal number of members across the different age groups. The sample size calculations showed that it was desirable to enrol about 200 participants to estimate a prevalence with a precision of ± 5%, at a 95% confidence interval (CI), within each age group[23]. The calculations were founded on the assumption that the prevalence for different mental health outcomes would not exceed 15% in the study population. We almost reached our target, ending up with 156-200 participants per age group. A flow chart of the sample selection is provided elsewhere[24].

Assessment and evaluation

Depression: Depression was assessed by the nine-item PHQ depression module (PHQ-9), with one item anchored to each of the nine symptoms required to establish a probable diagnosis of depression (*i.e.*, major depression and other depressive disorder) based on the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[18]. The PHQ-9 also matches the new DSM-V criteria[25]. The participants were presented a list of nine symptoms, and instructed to indicate how often they have experienced each symptom during the past two weeks. The response alternatives were: (0) "not at all"; (1) "several days"; (2) "more than half of the days"; and (3) "nearly every day". In the study, the PHQ-9 had a Cronbach's alpha of 0.84.

We categorized depressive disorders using the DSM-based diagnostic algorithm created by Spitzer *et al*[17]. To be classified with major depression, the algorithm requires that at least five symptoms are scored as 2 ("more than half of the days") (1,

"several days" for the suicidal ideation item), in which one of the symptoms is anhedonia or depressed mood. For other depressive disorders, two to four symptoms, including anhedonia or depressed mood, are endorsed with a score of at least 2 ("more than half of the days") ("several days" for suicidal ideation). A final item assesses functional limitations caused by the depressive symptoms, and in our study, it included the following four response alternatives: "No difficulties", "somewhat difficult", "very difficult", and "extremely difficult". We categorized the item into a dichotomous variable ("no difficulties", "difficulties").

Life satisfaction: Cantril's Ladder of Life Satisfaction was employed in the questionnaire to measure current life satisfaction[26]. The participants were asked to imagine a ladder with 10 steps, with the bottom step representing the worst possible life (a score of 1) and the top step representing the best possible life (a score of 10). The scale was treated as an untransformed continuous variable in the main analyses.

Referral to psychologist: During the study it became apparent that the need for professional help was large and unmet in the sample population. Based on early feedback we received from the participants, we decided to offer referrals for psychological counselling for the subsequent participants (421 of 736 participants). Patients were referred to psychological counselling for subjectively experienced mental disorder with the desire for professional help. The psychologist recorded the number of participants who met for counselling and the main themes of the consultations.

Independent variables: The participants were asked questions about their age (years: 18-35, 36-50, 51-65, ≥ 66), gender, education (years: < 11, 11-13, ≥ 14), native origin (Norwegian, non-Norwegian), place of residence (village/town, small or large city), the current status of their vision loss (stable, progressive), and whether they had other impairments (no, yes). Moreover, the severity of vision loss was assessed by asking the following question: "How good is your current vision (better-seeing eye, with glasses or contact lenses)". The question had the following response alternatives: "blind", "severely impaired", "moderately impaired", and "unspecified". As only 42 participants reported unspecified VI, we chose to merge the unspecified VI category with the category moderately impaired because we considered those participants to have a lower degree of vision loss than those who reported severe impairment and blindness. Lastly, we created an "age of VI onset" variable by subtracting the participant's age with the number of years since VI onset. The variable was categorized into the following three categories: "Congenital", "childhood/adolescence (2-24 years)", and "adulthood (≥ 25 years)".

Statistical analysis

All statistical analyses were performed using Stata Version 15 (Stata Corp., Texas, United States). The significance level was set at $P = 0.05$. Descriptive statistics included frequencies and percentages, and differences in frequency counts were assessed by Pearson's chi-squared or Fisher's exact tests. To account for the age-stratified sampling method, we tested in all analyses whether the estimates varied across the different age groups (years: 18-35, 36-50, 51-65, ≥ 66) by performing statistical analyses of cross-tabulated data or by including a product term between age and each independent variable in a regression model.

Depressive disorders involved major depression and other depressive disorders. We estimated the point prevalence and corresponding 95% exact CIs for all depressive disorders separately for women and men and for each of the four age groups. Next, to explore differences between classification methods, we performed supplementary analysis by using the sum score method of the PHQ-9 dichotomized into no or mild depression (a sum score < 10) and moderate to severe depression (a sum score ≥ 10)[18]. A sum score of 10 or higher has been recommended as the most optimal cut-off in screening for major depression[18,19].

Binomial generalized linear models with log-link function were used to derive unadjusted and adjusted estimates of associations between the independent variables (sociodemographic factors and VI characteristics) and depression[27]. The results were presented in terms of prevalence ratios (PRs) and 95%CIs. We did not include national origin and municipality size in the adjusted models because the full model resulted in less accurate estimates of the independent variables[28]. To reduce the risk of sparse data bias, we decided to model age (10-year intervals) and education as continuous variables. This decision had minor impact on the model fit.

The association between depression and life satisfaction was estimated using linear regression. The models were either unadjusted or adjusted for all indicated covariates. Our data m*et all* assumptions relating to linear regression, and we did not find any impact from outliers or multi-collinearity on the main results.

Statistical review

The statistical methods of the study were reviewed by Ragnhild Sørum Falk, PhD, Oslo University Hospital (e-mail: Rs@ous-hf.no).

RESULTS

A total of 1216 members were contacted, of which 736 participated (response rate: 61%). We had no additional sources of missing data; all participants answered all questions and none of the participants chose to withdraw from the study after completing the interviews. The characteristics of the VI population for women and men are listed in Table 1. Women were more likely than men to be of non-Norwegian origin and to have self-reported moderate VI. There were no gender differences in age, education, native origin, place of residence, onset-age or current status of vision loss, or whether the participants had any other impairments.

Point prevalence of depressive disorders

The results presented in Table 2 show the prevalence of depressive disorders in the VI population according to participants' age and gender. The point prevalence varied in different age groups between 4.2% and 15.6% for major depression (women: 5.6%-17.8%, men: 2.4%-12.9%), 4.0% and 6.2% for other depression (women: 3.8%-5.6%, men: 3.5%-7.1%), and 10.3% and 19.9% for any depression (women: 11.1%-22.8%, men: 9.4%-16.5%). Overall, the estimates were highest in the age group 36-50 years and lowest in the age group 66 years or above. There were no statistically significant differences between women and men (results not shown).

We then performed a supplementary analysis by estimating the proportion of the study population with moderate to severe levels of depression. Although this type of categorization resulted in higher rates of depression, the results from the analysis supported our main findings of severe depression being most prevalent among the youngest participants (Online Supplementary Table 1).

Associated factors of depression

The unadjusted and adjusted PRs for depressive disorders across different characteristics of the VI population are listed in Table 3. Having addition impairments, losing vision in adulthood, and having progressive vision loss were associated with a higher prevalence of depression in the unadjusted models. In contrast, lower rates of depression were found with older age. In the fully adjusted models, the PRs did not change much after adjusting for age, gender, education, and all indicated VI characteristics, except that the VI stability variable turned out to be non-significant. Depression was not related to gender, education or the severity of VI. There were no statistical interactions between age and any of the other independent variables ($P > 0.05$).

Functional limitations

Eighty-seven percent of depressed participants reported functional limitations in daily life, against 47% in those without depression. There was also a somewhat higher rate of functional limitations among depressed participants in the two youngest age groups (18-35 years and 36-50 years) than found among the older participants ($P = 0.10$).

Life satisfaction

The life satisfaction of participants with any depressive disorder was considerably lower than that of participants without depression (mean: 4.64 *vs* 7.18, β -2.54, 95%CI: -2.93, -2.16). The strength of the association remained similar after adjusting for age, gender, education, national origin, municipality size, and each of the four VI variables (β -2.36, 95%CI: -2.75, -1.98). None of the interactions involving age and the other independent variables reached statistical significance ($P > 0.05$).

Referral to a psychologist

Among the 421 participants that were offered mental health care, 45 (10.7%) participants had a consultation with a psychologist, with similar rates across the different age groups ($P = 0.91$). Of the 45 referred to counselling, 30 (8.4%) had no depression, 13 (28.9%) had major depression, and 2 (10.0%) had other depression ($P < 0.001$). The main themes of the consultations were related to minority stress and struggles in handling stigma that had been internalized in many cases. Other important themes were feelings of marginalization and the violation of basic human rights. Some participants described that having VI involved feelings of anxiety.

Table 1 Characteristics of the sample by gender

Characteristics	Total (*n* = 736), *n* (%)	Women (*n* = 403), *n* (%)	Men (*n* = 333), *n* (%)	*P* value[1]
Age[2]				0.93
18-35 yr	157 (21.3)	88 (21.8)	69 (20.7)	
36-50 yr	186 (25.3)	101 (25.1)	85 (25.5)	
51-65 yr	200 (27.2)	106 (26.3)	94 (28.2)	
≥ 66 yr	193 (26.2)	108 (26.8)	85 (25.5)	
Education				0.20
< 11 yr	115 (15.6)	69 (17.1)	46 (13.8)	
11-13 yr	286 (38.9)	162 (40.2)	124 (37.2)	
≥ 14 yr	335 (45.5)	172 (42.7)	163 (49.0)	
Native origin				0.006[b]
Norwegian	645 (87.6)	341 (84.6)	304 (91.3)	
Non-Norwegian	91 (12.4)	62 (15.4)	29 (8.7)	
Place of residence				0.21
Village/town	399 (54.2)	227 (56.3)	172 (51.7)	
Small or large city	337 (45.8)	176 (43.7)	161 (48.3)	
VI severity				0.05[a]
Moderate	254 (34.5)	155 (38.5)	99 (29.7)	
Severe	296 (40.2)	152 (37.7)	144 (43.2)	
Blindness	186 (25.3)	96 (23.8)	90 (27.0)	
Age of VI onset				0.24
Congenital	330 (44.8)	118 (46.7)	142 (42.6)	
Childhood/adolescence	142 (19.3)	69 (17.1)	73 (21.9)	
Adulthood	264 (35.9)	146 (36.2)	118 (35.4)	
Current VI status				0.06
Stable	523 (74.5)	275 (68.2)	248 (74.5)	
Progressive	213 (25.5)	128 (31.8)	85 (25.5)	
Other impairments				0.46
No	478 (64.9)	257 (63.8)	221 (66.4)	
Yes	258 (35.1)	146 (36.2)	112 (33.6)	

[a]$P < 0.05$.
[b]$P < 0.01$.
[1]*P*-value derived from Pearson's Chi-squared test.
[2]The sample had a mean age of 51.4 years (SD: 17.2), 51.7 for women and 51.1 for men. VI: Visual impairment.

DISCUSSION

Key findings

In our cross-sectional study we found that the prevalence of having any depressive disorder varied considerably across the four age groups, with 11%-23% in women and 9%-17% in men, and with highest rates for the youngest participants. Losing vision in adulthood and having addition impairments were found to be independently associated with increased rates of depression, whereas older age was associated with decreased rates. Furthermore, participants who were depressed had considerably lower life satisfaction compared with those who were not depressed.

Strengths and limitations

Our study is the largest study to date to address the prevalence of depression in VI populations across the entire adult age range, and the first to report estimates of other depressive disorder. The stratified sampling procedure made it possible to obtain robust depression estimates in all four age groups. The use of telephone interviews, the good response rate, and the lack of missing data increased the validity of the study findings.

Our study had also some limitations. First, it relied on cross-sectional data, which restricted our ability to make causal inferences about the observed associations. Second, the rates of PHQ-defined depressive disorders were not validated by a clinical interview and therefore the estimates reflected a probable diagnosis instead of

Table 2 The point prevalence of depressive disorders in the visual impairment population by age and gender

Disorders	Cases/total	Total (*n* = 736) (95%CI)	Women (*n* = 403) (95%CI)	Men (*n* = 333) (95%CI)
Major depression				
18-35 yr	18/157	11.5 (6.9, 17.5)	12.5 (6.4, 21.3)	10.1 (4.2, 19.8)
36-50 yr	29/186	15.6 (10.7, 21.6)	17.8 (10.9, 26.7)	12.9 (6.6, 22.0)
51-65 yr	14/200	7.0 (3.9, 11.5)	7.6 (3.3, 14.3)	6.4 (2.4, 13.4)
≥ 66 yr	8/193	4.2 (1.8, 8.0)	5.6 (2.1, 11.7)	2.4 (0.3, 8.2)
P value		0.003[b]	0.05[a]	0.08
Other depression				
18-35 yr	7/157	4.5 (1.8, 9.0)	4.6 (1.3, 11.2)	4.4 (0.9, 12.2)
36-50 yr	8/186	4.3 (1.9, 8.3)	5.0 (1.6, 11.2)	3.5 (0.7, 10.0)
51-65 yr	8/200	4.0 (1.7, 7.7)	3.8 (1.0, 9.4)	4.3 (1.2, 10.5)
≥ 66 yr	12/193	6.2 (3.3, 10.6)	5.6 (2.1, 11.7)	7.1 (2.6, 14.7)
P value		0.76	0.95	0.75
Any depression				
18-35 yr	25/157	15.9 (10.6, 22.6)	17.1 (9.9, 26.6)	14.5 (7.2, 25.0)
36-50 yr	37/186	19.9 (14.4, 26.4)	22.8 (15.0, 32.2)	16.5 (9.3, 26.1)
51-65 yr	22/200	11.0 (7.0, 16.2)	11.3 (6.0, 18.9)	10.6 (5.2, 18.7)
≥ 66 yr	20/193	10.3 (6.5, 15.6)	11.1 (5.9, 18.6)	9.4 (4.2, 17.7)
P value		0.07	0.59	0.16

[a]$P < 0.05$.
[b]$P < 0.01$.

diagnosed depression. Researchers have been concerned about the possibility that standard rating scales could overestimate the prevalence of depression in VI populations, given that certain depressive symptoms and especially somatic symptoms bear resemblance to complications of vision loss[4,7]. However, the PHQ algorithm method used in our study may produce fewer false positives than continuous cut-off scores, as it puts more weight on the core symptoms of depression (*i.e.*, depressed mood and anhedonia) and thus downplays the importance of somatic symptoms. Third, there was a potential risk of misclassification of the VI characteristics because some of the participants might not have known or been able to recall specific details about their condition. We expect non-differential misclassification, and in studies like ours, which include high-prevalent outcomes, the magnitude of the bias is likely to be low and drawn towards the null value[29]. Fourth, and lastly, because our sample was recruited from a member organization for the blind and partially sighted, it may be questioned whether it was representative of the broader VI population. However, the demographics of our sample were comparable with the 2015 census data of people with self-rated vision loss provided by Statistics Norway[30], except that our sample had a higher level of education. Since high levels of education may protect against the development of depression, we assume that the depression rates in our study were underestimated.

Comparison with the literature

To our knowledge, this is the first study of its kind to estimate the prevalence of depressive disorders in young and middle-aged adults with VI. The 16% and 20% rates in the respective age groups 18-35 years and 36-50 years were almost twice as high as those obtained in similar age groups in a survey of the general United States population in which depression was classified using the PHQ algorithm[28]. Furthermore, the prevalence rates of major depression in the same age groups were two to three times higher than the age-specific estimates for the general Western European population[13,14]. We also found that the youngest adults had worse outcomes than the older adults in terms of functional limitations. Our results illustrate that visually impaired adults of young or middle age are at particular risk of developing depressive disorders and that the demand for mental health care in these age groups is substantial.

The prevalence rates of depressive disorders or major depression in our two oldest age groups with VI were similar to those reported in earlier studies[4,5,7] or lower[9,10]. Furthermore, our depression rates did not differ from those reported elsewhere for older adults in the general Western European population[13,14]. These findings reflect

Table 3 Prevalence ratios for depressive disorders with sociodemographic factors and characteristics of visual impairment estimated using regression analysis (*n* = 736)

Variables	Any depressive disorder			
	Cases/total	%	Unadjusted PR (95%CI)	Adjusted PR (95%CI)
Age (continuous)[2]	-	-	0.89 (0.81, 0.99)[1]	0.83 (0.74, 0.93)[1]
Gender				
Men	42/333	12.6	1 [Reference]	1 [Reference]
Women	62/403	15.4	1.22 (0.85, 1.76)	1.17 (0.82, 1.68)
Education (continuous)	-	-	0.85 (0.72, 1.01)	0.86 (0.72, 1.02)
VI severity				
Moderate	40/254	15.8	1 [Reference]	1 [Reference]
Severe	44/296	14.9	0.94 (0.64, 1.40)	0.87 (0.60, 1.32)
Blind	20/186	10.8	0.68 (0.41, 1.13)	0.82 (0.49, 1.36)
Age of VI onset				
Congenital	35/330	10.6	1 [Reference]	1 [Reference]
Childhood/adolescence	26/142	18.3	1.73 (1.08, 2.76)[1]	1.63 (1.03, 2.58)[1]
Adulthood	43/264	16.3	1.54 (1.01, 2.33)[1]	1.76 (1.11, 2.79)[1]
Current VI status				
Stable	65/523	12.4	1 [Reference]	1 [Reference]
Progressive	39/213	18.3	1.47 (1.02, 2.12)[1]	1.43 (0.99, 2.06)
Other impairments				
No	50/478	10.5	1 [Reference]	1 [Reference]
Yes	54/258	20.9	2.00 (1.41, 2.85)[1]	1.88 (1.32, 2.67)[1]

[1]Results indicate statistical significance.
[2]Rescaled into 10-year age intervals. VI: Visual impairment; CI: Confidence interval; PR: Prevalence ratio.

the mixed results of previous studies of elderly adults in which the aim was to compare differences in estimates for visually impaired people and non-impaired people[5,7,10].

We found that adults who acquired VI late in life and adults with other impairments in addition to their vision loss had particularly high rates of depression. Vision loss may result in dramatic changes to people's lives and have implications for daily life activities, such as driving and travelling outside the home. Depression may develop as people struggle to cope with vision loss and its consequences for daily life[15,16]. Such challenges may be even greater for those with additional impairments. When people experience vision loss or receive a VI diagnosis, significant changes in self-esteem, self-efficacy, identity, social relations, and well-being may occur[31]. Many experience stress reactions such as shock, fear, frustration, helplessness, and grief[31], and their future life prospects become distorted. By contrast, those who have lost their vision earlier in life might have adapted to their vision loss during this period and accepted their life situation.

The high rates of depression in people with vision loss should be discussed also in the light of discrimination, stigmatization, alienation, and social isolation. Social interaction is considered an integral part of a fully-fledged life, and unmet needs could make life less pleasurable and less meaningful[32]. Loneliness and isolation are common in VI populations[33]. Also, those populations are more likely than their sighted peers to experience discrimination[34]. Exposure to negative social events may induce feelings of alienation, persistent negative thoughts and mood, distorted blaming of oneself and others, and loss of trust and faith in oneself and others[24]. Once people experience negative social events or social exclusion, they may become socially inactive or avoid certain situations in which they might experience further adverse events. This could become part of a downward spiral, resulting in isolation, loneliness, and depression[35].

We did not find any evidence of a relationship between self-reported VI severity and depression, which is consistent with the literature on this subject[7,9,11,20-22]. For example, in a survey of 1232 elderly outpatients from low vision rehabilitation services, van der Aa *et al*[7] did not find any differences in depression rates across the participants' degree of visual acuity loss. Direct or self-reported measures of visual functions may not capture the overall impact of a condition on people's daily lives[1],

and moderate vision loss may be as challenging to manage as a more severe one[31].

Our finding of a strong association between depression and lower life satisfaction is in accordance with documented findings relating to the general population[36,37]. Although causality may be reversed in that people who are less satisfied with life may be more likely be depressed, our findings probably point to the negative impact of depression on several life domains.

Implications

Our findings suggest that the risk of depressive disorders is high among young and middle-aged adults with VI. Vision loss can occur abruptly, resulting in a sudden loss of function, or it may develop gradually over a longer period, accompanied by the uncertainty about what the further development will cause. The high risk of depression should receive greater public attention, and special attention should be paid to adults of young age, the loss of vision in adulthood or those who have other impairments in addition to their vision loss. Preventive strategies, such as improved access to education, work, social services, and de-stigmatization programs, is also warranted. Ophthalmologists and other professionals who face people with vision loss should be aware of the high risk of depression and consider the need for referral to mental health care.

Quite unintentionally, our survey revealed an unmet need for consultations with a psychologist. People with vision loss may have a higher threshold when it comes to seeking help due to personal concerns such as a desire for self-reliance or avoidance of being labelled a "victim". More importantly, there is a lack of knowledge among health personal about the mental health adversities associated with VI[38], and to date, special mental health care services for people who are blind or have low vision is lacking in countries such as Norway. Thus, these issues should be addressed by both health care authorities and user organizations in cooperation.

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ARTICLE HIGHLIGHTS

Research background

People with visual impairment (VI) may be at risk of depression, but previous studies have demonstrated inconsistent results and have either reported extremely low rates or reported rates that ranged as high as 60%. Furthermore, previous studies of depression have mainly been restricted to older people or to specific subgroups of the population.

Research motivation

Depression in this population goes often unrecognized and untreated. We have yet to fully understand the magnitude of the problem and who is at particular risk of developing depression. By obtaining more precise knowledge about the age-specific prevalence and associated factors of depression, this information can be valuable in the design of preventive efforts and to anticipate service needs.

Research objectives

We conducted a large, age-stratified study in the adult population of people with low vision or blindness, with the following three main aims: (1) To estimate the point prevalence of depressive disorders in stratified age groups of adults with VI; (2) To examine whether depression was associated with different characteristics of vision loss; and (3) And to describe the association between depression and life satisfaction. By doing so, we hoped to examine and better understand the age-specific risk of depression among people with VI, as well as its associated factors and potential consequences on people's quality of life.

Research methods

The study was conducted as a cross-sectional interview-based survey between January and May 2017 and included an age-stratified sample of adults with VI. All participants were recruited through the members list of the Norwegian Association of the Blind and Partially Sighted. A total of 736 (61%) adults participated by completing the interview.

Research results

The prevalence of depression in different age groups varied from 11.1%-22.8% in women to 9.4%-16.5% in men. The estimates were highest in the two youngest age groups, and these rates were two times higher than those presented in previous studies of Westernized populations. Additionally, we found that depression was independently associated with having other impairments and loss of vision late in life, indicating that having difficulties in adapting to a new situation of being visually impaired or blind may put people at increased risk of developing depression. Lastly, depressed people in our study sample had considerably lower life satisfaction and were more likely to be referred for psychological counselling than were people without depression. The themes most often brought up by the participants during their consultations with the psychologist were related to problems with minority stress and handling stigma. We therefore argue that the high rates of depression in people with VI should be viewed in terms of stigma, discrimination, loneliness, and isolation.

Research conclusions

To our knowledge, our study is the first to provide estimates of depression for the youngest part of the adult VI population. We have identified some subgroups of the population at greater risk of depression than others. Because of the high depression rates and their strong associations with quality of life, we recommend the initiation of efforts that would improve access to professionals trained in the needs and challenges of people with VI.

Research perspectives

Our research findings should be supported by future studies that include a large probability sample of the entire adult VI population and that diagnose depression through clinical interviews. Moreover, future research should involve measures of modifiable risk factors of depression so that effective interventions can be designed to reduce the burden of depression for this population.

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Editorial board member of *World Journal of Psychiatry*, Dr. Löffler-Stastka is the Dean for Postgraduate Programs Medical University Vienna, Head of the University Program for Psychotherapy Research, Head of the University Program for Health Care Management, University Professor for Psychoanalysis and Psychotherapy, Training Therapist for Psychoanalytic Psychotherapy. She studies on process-outcome research, assessment tools, psychotherapeutic/medical care, therapist variable (attitude, countertransference, empathy, mentalization, micro-expressions, therapeutic competencies) and research concerning educational and training issues. Mid career counselor of the SPRISTAD group/Society for Psychotherapy Research. Besides, studies concerning competence development will go on in several settings, conceptual research leads to discussions about competencies that are relevant for neighbouring disciplines and policies.

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ORIGINAL ARTICLE

Basic Study

Comparison of three administration modes for establishing a zebrafish seizure model induced by N-Methyl-D-aspartic acid

Xin-Yi Long, Shuang Wang, Zhi-Wen Luo, Xu Zhang, Hong Xu

ORCID number: Xin-Yi Long 0000-0003-0265-9645; Wang Shuang 0002-0002-6053-3998; Zhi-Wen Luo 0000-0002-0524-9951; Xu Zhang 0000-0001-8916-5626; Hong Xu 0000-0003-4938-0203.

Author contributions: Long XY, Wang S, Luo ZW and Zhang X conceived the study; Wang S, Long XY and Luo ZW performed the experiments; Long XY, Wang S and Luo ZW analyzed the data; Luo ZW, Wang S and Long XY drafted the manuscript; All authors read and approved the final version of the manuscript; Xu H provided the idea and funding; Long XY and Wang S contributed equally.

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Xin-Yi Long, Shuang Wang, Queen Mary School of Nanchang University, Nanchang 330006, Jiangxi Province, China

Zhi-Wen Luo, Department of Sports Medicine, Huashan Hospital, Fudan University, Shanghai 200433, China

Xu Zhang, Affiliated Eye Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

Hong Xu, Institute of Life Science, Nanchang University, Nanchang 330031, Jiangxi Province, China

Corresponding author: Hong Xu, PhD, Professor, Institute of Life Science, Nanchang University, Xuefu Avenue 1299, Nanchang 330031, Jiangxi Province, China.
xuhong@ncu.edu.cn

Abstract

BACKGROUND

Epilepsy is a complex neurological disorder characterized by recurrent, unprovoked seizures resulting from the sudden abnormal discharge of brain neurons. It leads to transient brain dysfunction, manifested by abnormal physical movements and consciousness. It can occur at any age, affecting approximately 65 million worldwide, one third of which are still estimated to suffer from refractory seizures. There is an urgent need for further establishment of seizure models in animals, which provides an approach to model epilepsy and could be used to identify novel anti-epileptic therapeutics in the future.

AIM

To compare three administration modes for establishing a seizure model caused by N-Methyl-D-aspartic acid (NMDA) in zebrafish.

METHODS

Three administration routes of NMDA, including immersion, intravitreal injection and intraperitoneal injection, were compared with regard to their effects on inducing seizure-like behaviors in adult zebrafish. We evaluated neurotoxicity by observing behavioral changes in zebrafish and graded those behaviors with a seizure score. In addition, the protective effects of MK-801 (Dizocilpine) and

authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

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natural active constituent resveratrol against NMDA-induced alterations were studied.

RESULTS
The three NMDA-administration methods triggered different patterns of the epileptic process in adult zebrafish. Seizure scores were increased after increasing NMDA concentration regardless of the mode of administration. However, the curve of immersion continuously rose to a high plateau (after 50 min), while the curves of intravitreal injection and intraperitoneal injection showed a spike in the early stage (10-20 min) followed by a steady decrease in seizure scores. Furthermore, pretreatment with resveratrol and MK-801 significantly delayed seizure onset time and lowered seizure scores.

CONCLUSION
By comparing the three methods of administration, intravitreal injection of NMDA was the most suitable for establishing an acute epileptic model in zebrafish. Thus, intraperitoneal injection in zebrafish can be applied to simulate diseases such as epilepsy. In addition, NMDA immersion may be an appropriate method to induce persistent seizures. Moreover, MK-801 and resveratrol showed strong anti-epileptic effects; thus, both of them may be clinically valuable treatments for epilepsy.

Key words: Seizure; Zebrafish; N-Methyl-D-aspartic acid; Administration modes; Resveratrol; MK-801

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Core tip: This is the first study to systematically compare the three main administration modes to establish a seizure model in zebrafish. A newly developed zebrafish model with acute and sustained experimental epileptic behavior enables us to study and identify potential mechanisms and screen anti-epileptic drugs. Direct administration of N-Methyl-D-aspartic acid stimulates abnormal excitations of brain nerve cells to simulate epileptic seizures. This study demonstrated that intravitreal injection can be used to establish an acute epilepsy model and immersion can be used as a persistent epilepsy model. The protective effects of resveratrol and MK-801 on the epileptic process were also confirmed, which may have clinical application value.

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INTRODUCTION

Epilepsy is a chronic brain disorder caused by abnormal, excessive and synchronous neuronal activities in the brain. The clinical manifestations are characterized by paroxysmal, transient, repetitive and stereotyped. The location of abnormal discharge neurons and the range of abnormal discharge spread are different, leading to different forms of seizure, manifested as sensory, motor, conscious, mental, behavioral, autonomic dysfunction or a combination of multiple dysfunctions[1]. According to the World Health Organization report, there are many causes of epilepsy, such as stroke, brain trauma, and central nervous system infection[2]. Although it is generally believed that about two-thirds of epilepsy is idiopathic, most of which are now considered to be hereditary[1]. Epilepsy also has various psychiatric complications such as depression, anxiety and cognitive defects[3,4]. It has been reported that peroxisome proliferator-activated receptor γ and mutations in genes involved in GABA-mediated inhibitory neurotransmission are highly associated with the pathogenesis of epilepsy[1,5]. Moreover, it is widely accepted that glutamate overstimulation of the N-Methyl-D-aspartic acid (NMDA) receptor is an important pathogenesis of epilepsy, which leads

to continuous internal flow of calcium ions and excessive excitement of the hippocampal networks[6,7]. The molecular mechanism of epilepsy is still not fully understood, and thus there is a lack of effective clinical treatment[8,9]. Therefore, building relevant preclinical models is imperative for therapeutics screening in this disease.

NMDA is an amino acid derivative that exists naturally in the animal body. It is an analog of L-glutamate, an important excitatory neurotransmitter in the mammalian central nervous system. It has been used to model a series of neurodegenerative diseases such as epilepsy, glaucoma, Alzheimer's disease, Parkinson's disease and Huntington's disease[10-15]. NMDA-induced cellular excitotoxicity may be the consequence of overstimulating NMDA receptors at high concentrations of NMDA, causing a massive calcium influx. The overproduction of nucleases, proteinases, lipase, free radicals as well as the activation of nitric oxide pathway ultimately then give rise to cell death[16,17].

As a vertebrate model, zebrafish have received a great deal of attention in the field of developmental biology and genetics over the last decade as a cost-efficient and relevant alternative for human disease modeling and large-scale drug screening[18]. There are many reasons for its popularity, for example, zebrafish share high genetic, cellular and organ homologies to humans over the evolutionary process[19]. Besides their homology, zebrafish are much easier to breed than other types of experimental animals due to ease of handling and fast reproduction rate. These advantages indicate that zebrafish has outstanding value in preclinical drug screening[20,21]. Furthermore, its central nervous system is structurally similar to that of mammals. Some signaling systems such as serotonin energy and GABAergic neurotransmission are also highly similar[18,22]. When it comes to studying brain disease, these aspects have always been the advantages of zebrafish. Establishing a reliable zebrafish epilepsy model not only contributes to a better understanding of the molecular pathology of zebrafish seizures, but may also be conducive to screen drugs that protect the brain from seizure damage. Both of these directions will contribute to better clinical treatment of epilepsy.

The principal methods of administration used in the present study were immersion, intravitreal injection and intraperitoneal injection. Some studies have demonstrated that drugs can be absorbed directly from the water environment through the skin of zebrafish[23,24], while intraperitoneal injection of drugs can induce epileptic behaviors in zebrafish[25,26]. Ouabain was injected into the eyeballs of zebrafish through the vitreous cavity, resulting in nerve cell damage[27,28]. Although there are other alternative modeling methods, such as intraperitoneal perfusion, they were not adopted in this study.

MK-801 is a non-competitive antagonist of the NMDA receptor and can directly prevent NMDA-induced excitatory toxicity. Therefore, it was used as a positive control. Resveratrol is a biologically active constituent extracted from many plants. As previously reported, it has a multitude of health benefits including the ability to prolong life and prevent certain diseases such as heart disease, autoimmune diseases, metabolic disorders[29], inflammation[30], neurodegeneration[31,32], and epilepsy[33,34]. In addition, it also plays an active role in retinal degeneration models[35]. However, it is not clear whether the three modes of NMDA administration cause changes in epileptic behavior, and whether resveratrol or MK-801 can protect against this brain disorder. This study aims to investigate these two key aspects to further understand the establishment of seizure models in zebrafish and lay the foundation for drug screening and treatment development.

MATERIALS AND METHODS

Animals

The study was approved by the Ethical Review Committee of Nanchang University (Nanchang, Jiangxi Province, China). The China Zebrafish Resource Center (Wuhan, Hubei Province, China) provided adult male and female wild-type zebrafish (*Danio rerio*, AB strain). All adult zebrafish were raised in a temperature-controlled (28°C) zebrafish breeding system (Thmorgan Biotechnology Corp., Ltd. Beijing, China) and all zebrafish were propagated in a cycle of 14 h light/10 h dark in the experiment, and they were fed with brine shrimp twice daily (Wudi, Shandong Province, China).

Treatments

NMDA (M3262, Sigma, United States) was dissolved in phosphate buffered saline (PBS) to prepare solutions for different modeling methods (immersion: 300 and 500

μmol/L; intraperitoneal injection: 8 and 16 mg/kg; intravitreal injection: 0.1 and 0.5 mol/L). MK-801 (M107, Sigma, United States) was soluble in 500 mL/L ethanol (intraperitoneal injection: 3 mg/kg, intravitreal injection: 0.05 mol/L). Resveratrol (R5010, Sigma, United States) was dissolved in 1000 mL/L ethanol and kept in the dark during storage and during the whole experiment (40 mg/L). Distilled water was used to dissolve MS-222 (A5040, Sigma, United States) (0.2 g/L). The timeline of drug delivery is shown in Figure 1.

Study design

Immersion: Before NMDA treatment, zebrafish were soaked in resveratrol solution for 1 d in advance. Resveratrol was dissolved in 10 μL of 1000 mL/L ethanol, and then mixed with 100 mL of distilled water for 1 h until completely dissolved. During resveratrol treatment, the reaction tank was completely covered to avoid photodegradation of the compound. Then adult zebrafish (n = 6 in each group) were immersed in 500 μmol/L NMDA solution for 1 h (the solution was prepared at 28°C) and seizure-like behaviors were observed for 1 h. Another two groups of zebrafish, 12 in total without resveratrol immersion were separately placed into the other two 2 L tanks, respectively, filled with 300 μmol/L and 500 μmol/L concentration of NMDA for 1 h to record behavioral changes. Zebrafish in the MK-801 group were intraperitoneally injected with 10 μL MK-801 1 h before 500 μmol/L NMDA immersion. The remaining zebrafish were set as the control group, and except for drug treatment, the rest of the process was the same as the experimental groups.

Intravitreal injection: Zebrafish were anesthetized with MS-222 before intravitreal injection. According to previous research methods, the volume of the vitreous cavity measured by digital caliper is approximately 200-500 nL[36]. In the preliminary experiment to determine the appropriate amount of injection, we found that 100 nL PBS did not cause any retinal damage or behavior changes in zebrafish. The freshly prepared 100 nL of 0.1 and 0.5 mol/L NMDA solution was then aspirated with an acupuncture needle (0.20 mm) and inserted through a small incision between the vitreous body and the retina and delivered into the right eyes of zebrafish. The syringe pumps (HARVARD, C-14171) helped to deliver the appropriate amount of NMDA. The drug treatment time was 1 h. For the resveratrol + NMDA group, these zebrafish were treated with resveratrol for 1 d before 0.5 mol/L NMDA injection. In the 0.5 mol/L NMDA + MK-801 group, 100 nL MK-801 was injected intravitreally. 1× PBS injection was performed in the same manner to the control group. After the injection, all the fish were kept out for at least 1 min to allow for drug absorption and then returned to their normal living environment to record their behaviors.

Intraperitoneal injection: Each zebrafish was weighed before the injection and then adult zebrafish were anesthetized with MS-222 solution. NMDA 8 mg/kg and 16 mg/kg (the doses used here were chosen by comparing those used in rodents) was carefully injected into the abdomen in the operating area when the zebrafish temporarily lost body control. For the resveratrol + NMDA group, these zebrafish were treated with resveratrol for 1 d before the NMDA injection. Next, 10 μL MK-801 was injected intraperitoneally in the NMDA+MK-801 group. The remaining fish were injected with 1× PBS and set as the control group. Their 1 h behaviors were recorded *via* camera.

Seizure score

Following intravitreal and intraperitoneal injection, the zebrafish were individually placed into 2 L tanks after NMDA treatment; for immersion, the fish were directly placed in 2 L NMDA solution. We manipulated a specific camera to monitor the behavior of each fish to determine its seizure score. The behaviors of all zebrafish were photographed for 60 min to assess the degree of epilepsy. The seizure score was quantified by the following criteria: 1 point, immobility and hyperventilation; 2 points, whirlpool swimming; 3 points, rapid movement from right to left; 4 points, abnormal and spastic muscle contraction; 5 points, rapid clonic convulsion of the whole body; 6 points, submergence and spasm for several minutes; 7 points, death[25].

Statistical analysis

Statistical analysis was performed based on records to calculate time points and duration of abnormal behavior in zebrafish. The experimental data were expressed as mean ± SE. All data were analyzed by t-test using GraphPad PRISM 7.00. ANOVA was then performed to assess the differences in seizure and latency between the experimental groups, with $P < 0.05$ considered statistically significant.

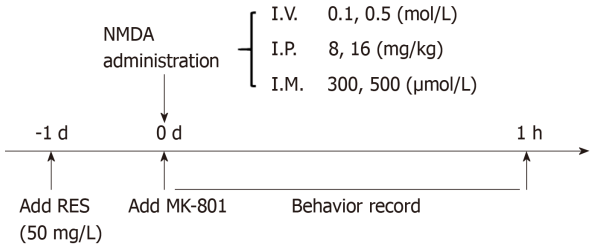


Figure 1 Experimental protocols. Three administration modes were used in this study, including intravitreal injection, intraperitoneal injection and immersion. All resveratrol treatments were carried out 1 d before N-Methyl-D-aspartic acid (NMDA) treatment. Behavior records began immediately after NMDA and MK-801 treatment, which lasted for 1 h. NMDA: N-Methyl-D-aspartic acid; I.V.: Intravitreal injection; I.P.: Intraperitoneal injection; I.M.: Immersion.

RESULTS

Intravitreal injection

Prior to NMDA treatment, zebrafish were immersed in 40 mg/L resveratrol for 1 d. Zebrafish behavior was then observed and recorded for 60 min after intravitreal injection of NMDA and graded by the seizure score. NMDA treatment caused a seizure-like syndrome characterized by rapid movement, jumping, swimming in circles, and an intense response to stimulation. As shown in Figure 2A, the overall curve presented a trend of an intial rise and then a decrease, and the highest seizure score was approximately up to 5. The mean seizure score in the high-dose (0.5 mol/L) NMDA treatment group was significantly higher than that in the low-dose (0.1 mol/L) NMDA treatment group (4 *vs* 2, $P < 0.0001$), while co-injection of 50 mmol/L MK-801 with 100 nL 0.5 mol/L NMDA decreased the score to lower than 2. The shortest seizure onset time in zebrafish given intravitreal injection was about 3 min in the high-dose NMDA group. Additionally, the seizure onset time following high-dose NMDA treatment was significantly prolonged by MK-801 (> 10 min), to a level even lower than that of low-dose (0.1 mol/L) NMDA treatment (Figure 2B). Pretreatment with resveratrol also lowered the seizure score from approximately 4 to 1 and significantly delayed seizure onset from 3 to around 7 min ($P = 0.0024$) (Figure 2A and B). These behavioral changes indicate that intravitreal injection of NMDA leads to seizure-like behavior in zebrafish within a short time that can be significantly prevented by resveratrol pretreatment, consistent with prior studies showing the anti-epileptic effects of resveratrol.

Intraperitoneal injection

For resveratrol pretreatment, we immersed zebrafish in 50 mg/kg resveratrol for 1 d and then performed intraperitoneal injection of NMDA. Zebrafish behaviors were recorded for 60 min, and were similar to those following intravitreal injection of NMDA. According to the analysis of seizure score, the overall curve first increased within 30 min and then decreased following intraperitoneal injection. The degree of epilepsy in zebrafish injected with high dose NMDA was significantly higher than that in zebrafish injected with low dose NMDA. The seizure score in the high-dose (16 mg/kg) NMDA group was 4-5, while the low-dose (8 mg/kg) group had a score of around 2 (Figure 3A). The same trend in seizure onset time was identified: 16 mg/kg NMDA-treated zebrafish had a seizure onset time of less than 10 min while the 8 mg/kg NMDA-treated group had a seizure onset time closer to 20 min (Figure 3B). On the other hand, zebrafish treated intraperitoneally with 10 μL 3 mg/kg MK-801 + high-dose NMDA, had a significantly reduced seizure score at all time points analyzed ($P < 0.001$) (Figure 3A) as well as a very significantly delayed seizure onset time (from approximately 6 min to over 30 min) ($P < 0.001$) (Figure 3B). Resveratrol pretreatment also had a highly significant effect in lowering the seizure score from approximately 5 to 2 min (Figure 3A) and delayed seizure onset time from around 4 min to about 8 min ($P = 0.0024$) (Figure 3B). These data indicate that seizures can be more intensely induced in zebrafish by intraperitoneal injection of NMDA as well as intravitreal injection and that MK-801 and resveratrol have anti-epileptic effects in this model system.

Immersion

Zebrafish in one experimental group were placed into 2 L tanks with 40 mg/L resveratrol for 1 d before NMDA immersion. By recording zebrafish behaviors over 60 min, we found that different groups almost showed an increasing trend. Seizure scores

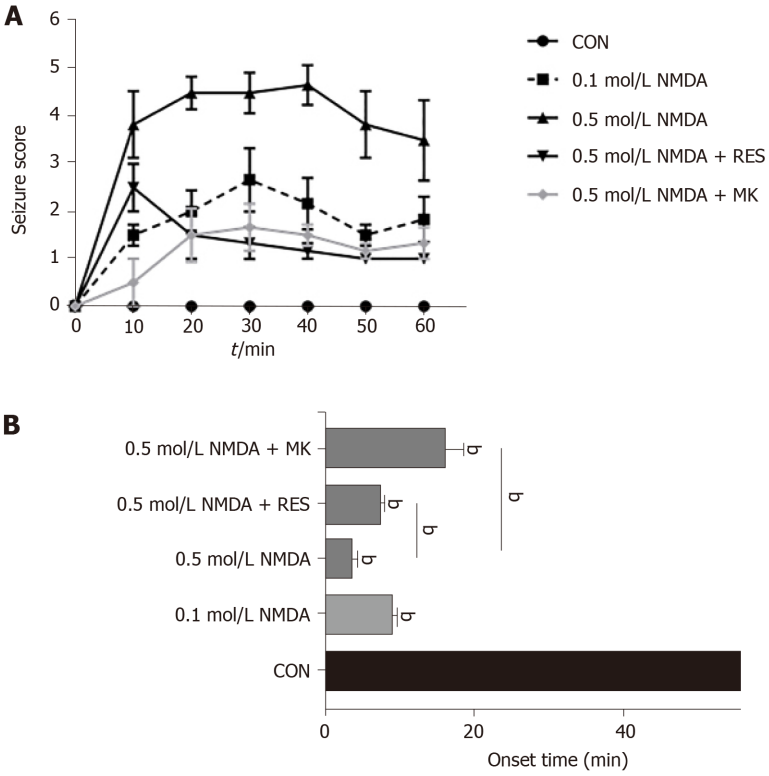


Figure 2 Intravitreal injection of N-Methyl-D-aspartic acid causes acute seizure-like behavior in zebrafish. Seizure activity and onset scores following N-Methyl-D-aspartic acid (NMDA)-intravitreal injection (0.1 mol/L and 0.5 mol/L, 50 mg/L resveratrol + 0.5 mol/L NMDA, and 50 mmol/L MK-801 + 0.5 mol/L NMDA). A: The mean seizure scores (± SE) for each treatment group plotted against time after NMDA injection; B: The latency of seizure onset after NMDA injection. Bars represent mean ± SE of the time lag to the onset of the first convulsion in each group. Data were analyzed using one-way ANOVA and *t*-test for the different groups (n = 6) ($^bP < 0.01$ *vs* control). NMDA: N-Methyl-D-aspartic acid; RES: Resveratrol; MK: MK-801.

continued to rise steadily within 0-20 min and 30-50 min. In addition, seizure scores following high-dose NMDA immersion were statistically higher than those following low-dose NMDA immersion. High-dose (500 μmol/L) NMDA treatment resulted in a seizure score of 2-4 while low-dose (300 μmol/L) treatment resulted in a score of around 1 to 2 (Figure 4A). The same trend was identified for seizure onset time: The 500 μmol/L NMDA-treated group had a seizure onset time of fewer than 5 min, while the 300 μmol/L NMDA-treated group had a seizure onset time of nearly 10 min (Figure 4B). On the other hand, zebrafish immersed in high-dose NMDA after 10 μL 3 mg/kg MK-801, had a significantly reduced seizure score at all time points analyzed ($P < 0.001$) (Figure 4A) as well as a delayed seizure onset time (from approximately 5 min to 9 min) ($P < 0.001$) (Figure 4B). Resveratrol pretreatment also had a highly significant effect in lowering the seizure score from approximately 4 to 1 (Figure 4A) and delayed seizure onset time from around 5 min to about 10 min ($P = 0.0024$) (Figure 4B). These data indicate that seizures can be induced in zebrafish by immersion in NMDA in a slow and unremitting way and that MK-801 and resveratrol have anti-epileptic effects in this model system.

Comparison of the three administration modes

By comparing 1 h seizure scores and onset time of the three administration modes, we found high-dose NMDA immersion maintained the seizure score at about 2.5 to 3.5, the score caused by intraperitoneal injection was 4 to 5, and that following intravitreal injection was maintained at approximately 3.2 to 4.8 (Figure 5A). The trend in epilepsy caused by the three modes of administration generally increased initially and then decreased. In addition, the most severe stage of epilepsy caused by intraperitoneal injection of high-dose NMDA took about 30 min, while intravitreal injection took 40 min and immersion took 50 min. With regard to seizure onset time, immersion had the longest onset time of the three methods (approximately 6.3 min), which was followed by intraperitoneal injection (5.5 min). Intravitreal injection induced seizure-like behaviors within 3 min ($P < 0.001$) (Figure 5B). These data show that NMDA induces epilepsy-like behavior, while administration patterns alter seizure progression of

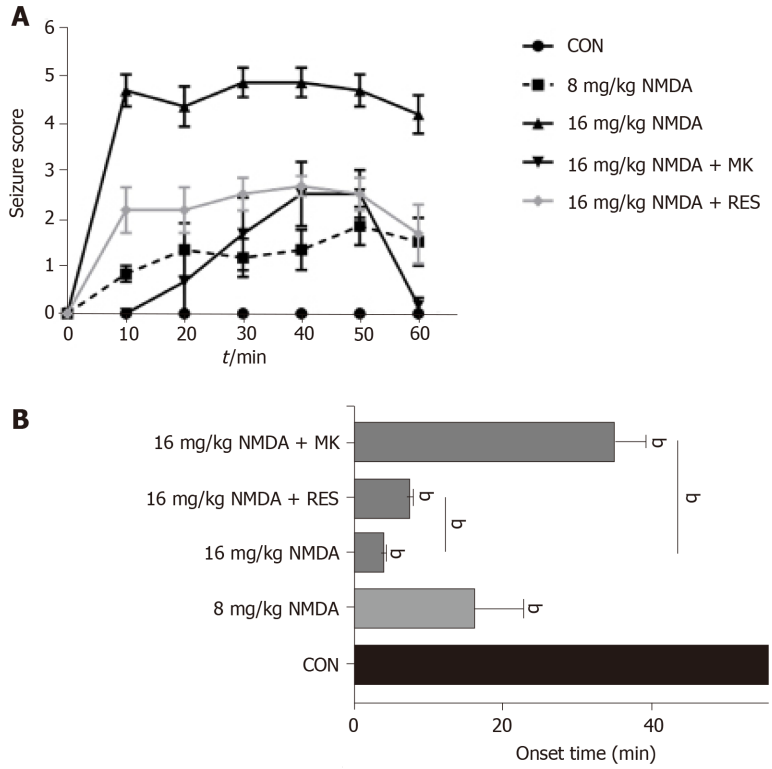


Figure 3 Intraperitoneal injection of N-Methyl-D-aspartic acid causes acute seizure-like behavior in zebrafish. Seizure activity scores and onset times following N-Methyl-D-aspartic acid (NMDA)-intraperitoneal injection (8 and 16 mg/kg, 50 mg/L resveratrol + 16 mg/kg NMDA, and 3 mg/kg MK-801 + 16 mg/kg NMDA). A: The mean seizure scores (± SE) for each group plotted against time after NMDA injection; B: The latency of seizure onset after NMDA injection. Bars represent mean ± SE of the time lag to the onset of the first convulsion in each group. Data were analyzed using one-way ANOVA and *t*-test for the different groups ($n = 6$) ($^{b}P < 0.01$ *vs* control). NMDA: N-Methyl-D-aspartic acid; RES: Resveratrol; MK: MK-801.

epilepsy diversely.

DISCUSSION

Numerous animal models have been used in epilepsy research. However, choosing the best experimental model mainly depends on the problem to be solved, the type of epilepsy simulated, whether it is consistent with the clinical characteristics, and whether it is simple and reliable. Therefore, selecting an appropriate and valuable animal model of epilepsy is undoubtedly an effective shortcut to better study the mechanism and treatment of epilepsy. Our preliminary experiment showed that intravitreal injection, intraperitoneal injection, and immersion all caused seizure-like behaviors in zebrafish. By using different NMDA concentrations, we utilized these three methods of drug delivery to establish seizure models associated with brain damage, which are also less harmful to adult zebrafish.

It has been reported that intravitreal injection of NMDA induces seizure-like behaviors in zebrafish. We found that intravitreal injection of NMDA was the most suitable for the establishment of an acute seizure model in zebrafish, as it caused seizure-like manifestations in a short time with a high concentration of NMDA in the central nervous system, which greatly reduces drug waste and shortens the time to disease. Intraperitoneal injection of NMDA did cause seizure-like behavioral changes in adult zebrafish, which was similar to analogous seizure models in rodents[37,38]. The effect caused by this method depends on the amount of NMDA injected due to strong intestinal absorptive capacity. When comparing the three modeling methods, immersion was less harmful to zebrafish in a short period of time and hence contributes to observing long-term and chronic epileptic behavior. As the drug was directly dissolved in water, and zebrafish can continuously take in the drug from the surrounding environment, the efficacy or toxicity of drugs is not observed in mammals and can be observed using this methd in a short time.

However, these three methods still have some limitations. Although intravitreal

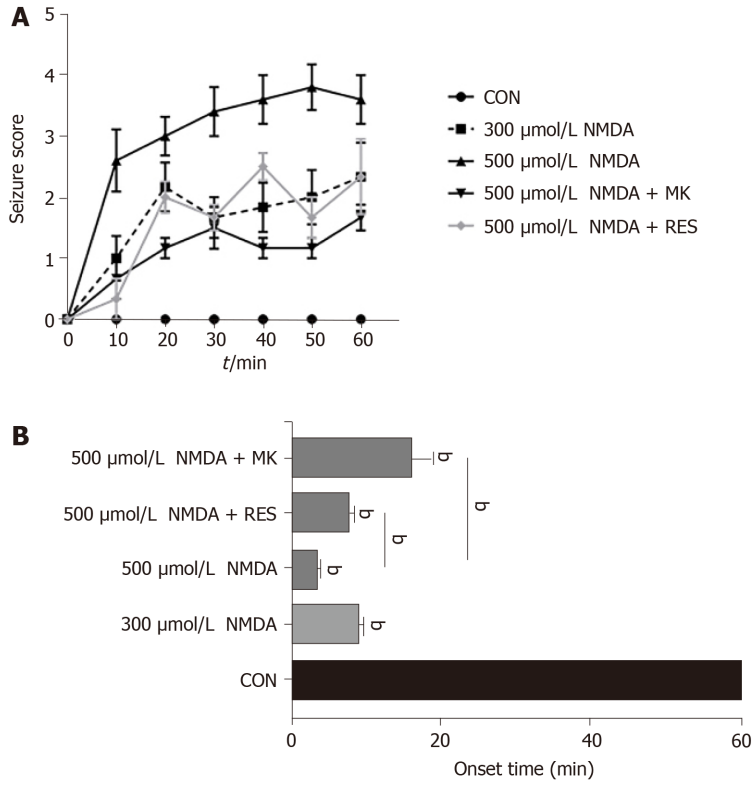


Figure 4 Immersion of N-Methyl-D-aspartic acid causes persistent seizure-like behavior in zebrafish. Seizure activity scores and onset times following N-Methyl-D-aspartic acid (NMDA)-immersion (300 μmol/L and 500 μmol/L NMDA, 40 mg/L resveratrol + 500 μmol/L NMDA, and 3 mg/kg MK-801 + 500 μmol/L NMDA). A: The mean seizure scores (± SE) for each group plotted against time after NMDA immersion; B: The latency of seizure onset after NMDA immersion. Bars represent mean ± SE of the time lag to the onset of the first convulsion in each group. Data were analyzed using one-way ANOVA and *t*-test for the different groups (n = 6) ($^aP < 0.05$, $^bP < 0.01$ *vs* control). NMDA: N-Methyl-D-aspartic acid; RES: Resveratrol; MK: MK-801.

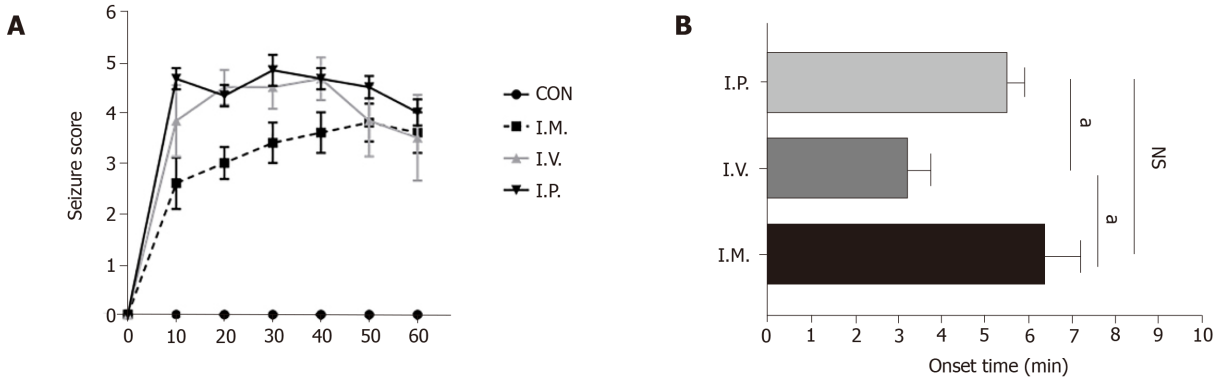


Figure 5 Comparison of the three administration routes on seizure score and onset time. Seizure activity scores and onset times following intravitreal injection, intraperitoneal injection and immersion with 0.5 mol/L, 16 mg/kg and 500 μmol/L N-Methyl-D-aspartic acid (NMDA), respectively. A: The mean seizure scores (± SE) for each route plotted against time after NMDA treatment; B: The latency of seizure onset after NMDA treatment. Bars represent mean ± SE of the time lag to the onset of the first convulsion using each method. Data were analyzed using one-way ANOVA and *t*-test for the different routes (n = 6) ($^aP < 0.05$). NMDA: N-Methyl-D-aspartic acid; I.V.: Intravitreal injection; I.P.: Intraperitoneal injection; I.M.: Immersion.

injection of NMDA exerts the same effect on zebrafish as other animal models, the difficulty of microinjection may hinder its application in drug screening. Therefore, to improve the potential of this model system, it is necessary to perfect each detailed procedure. In addition, the ocular pharmacokinetics of different drugs are sensitive to different clearance mechanisms[39], which is mainly affected by the permeability of retinal pigment epithelium. Understanding the clearance mechanism of different drugs in zebrafish will ensure the effectiveness of drug delivery, which provides a basis for ideal animal modeling and further drug screening. Intraperitoneal

administration is relatively easy, but it is worth noting that the procedure demands care in order to avoid injury to zebrafish organs such as the heart. With respect to the operational skills, immersion requires only control of the drug concentration.

According to the results of induced behavior changes, all three delivery modes were effective in delivering NMDA to the brain. Given that immersion lasts longer and takes effect later, the effects induced by intraperitoneal and intravitreal injection of NMDA on zebrafish appeared earlier. We hypothesized that intraperitoneal and vitreous injection would cause a sharp increase in NMDA concentration in the blood and target cells, resulting in acute pathophysiological changes, but NMDA concentration would then drop rapidly to baseline levels, and thus the dramatic response would quickly disappear. Of these three administration modes, the seizures induced by intravitreal injection appeared faster than the other two modes, which suggests that different administration routes into the zebrafish capillary network may have distinct effects of drug delivery. Intraperitoneal injection of NMDA has poor target specificity, rendering it hard to accumulate in the brain, and this drawback may cause uncontrollable damage to other non-targeted organs, such as the heart, which can interfere with the experiment results. In contrast, immersion can result in a relatively steady increase in NMDA concentration in the blood, which is enough to cause a long-term epileptic response; therefore, is more suitable for the model of sustained epilepsy. Unfortunately, due to the late onset time of seizures induced by drug immersion, it is not suitable for large-scale drug screening. At the operational level, immersion is the simplest and most convenient way to administer drugs, while intravitreal injection is relatively complicated but also the most effective way to establish the zebrafish model of brain disorder.

Antisense morpholine oligonucleotides (MOs) and hyperthermia have been used to construct zebrafish epilepsy models in previous studies. Although MOs can effectively interfere with protein synthesis of target genes, it can induce p53-dependent apoptosis and non-targeted cell-specific effects in gene expression, which in turn affect behavioral phenotype analysis[40]. The hyperthermia-induced zebrafish seizure model is more suitable for studying the mechanism of epileptic seizures *in vivo* and for acute seizure of chronic processes, but it does not show any persistence[41]. Both methods are appropriate for studying the mechanism of zebrafish seizures during innate or embryonic development. However, the methods we use can be applied to study the process of seizures in adulthood. Not only can they induce characteristic seizures which are similar to the reactions observed in mammalian seizures, but also emphasize the role of the zebrafish model in glutamate excitatory neurotransmission. For example, clomizole (a histamine receptor antagonist) is effective for gene-induced epilepsy of SCN1lab zebrafish (a model of Dravet syndrome caused by *SCN1a* mutation), a persistent drug-resistant epilepsy[42]. In addition, the methods we proposed can screen out the effect of psychotropic drugs and toxicity in the animal at a glance and reduce twists and turns in the drug development process.

It is noteworthy that one main defect in this NMDA-induced neurotoxicity model is that it only focuses on a single pathological mechanism (glutamate excitotoxicity) of epileptic seizures. Considering that the pathogenesis of human epilepsy is more complex, these models may not fully represent the pathogenesis of epilepsy; thus, may not be used to carry out clinical research on effective treatment methods for epilepsy[43]. In the current study, we only focused on seizure-like behavioral changes but did not carry out a specific analysis of pathological brain alterations or distortion of electrical signal transduction caused by excessive glutamate signaling. Therefore, further research is needed to fully establish the intravitreal administration route as a relevant model of epilepsy and other brain diseases. Although zebrafish seizure models are valuable for discovering anticonvulsants and studying ictogenesis, they are inadequate for the entire disease process. When studying epilepsy and screening anti-epileptic drugs, there is still a lack of epilepsy models that truly reflect the pathogenesis and characteristics of different forms of human epilepsy.

In conclusion, these results show that intravitreal injection of NMDA is an effective model for inducing acute epilepsy in zebrafish, and NMDA immersion can be used as a suitable model for persistent epilepsy. Additionally, intravitreal and intraperitoneal injection of NMDA may both be useful for modeling epilepsy. By comparing the three different drug administration patterns comprehensively, these models are valuable for identifying the potential mechanisms of epilepsy and drug screening. Last but not the least, our study provides convincing evidence for the potential application of MK-801 and resveratrol, a safe plant extract which is available for the treatment of epilepsy.

ARTICLE HIGHLIGHTS

Research background

Epilepsy is a complex neurological disorder characterized by recurrent, unprovoked seizures resulting from the sudden abnormal discharge of brain neurons. It leads to transient brain dysfunction, manifested by abnormal physical movements and consciousness. It can occur at any age, affecting approximately 65 million worldwide, one third of which are still estimated to suffer from refractory seizures. The molecular mechanism of epilepsy is still not fully understood; thus, there is a lack of effective clinical treatment. Therefore, building relevant preclinical models is imperative for screening therapeutics for this disease.

Research motivation

There is an urgent need for further establishment of seizure models in animals, including acute epilepsy models and persistent epilepsy models. These models could be used to study the mechanism of epilepsy and identify novel anti-epileptic therapeutics in the future.

Research objectives

The main objective was to compare three administration modes for establishing a seizure model caused by N-Methyl-D-aspartic acid (NMDA) in zebrafish.

Research methods

Three administration modes of NMDA, including immersion, intravitreal injection and intraperitoneal injection, were compared with regard to their effects on inducing seizure-like behaviors in adult zebrafish. We evaluated neurotoxicity by observing behavioral changes in zebrafish and graded those behaviors with a seizure score. Statistical analysis was performed based on records to calculate time points and duration of abnormal behavior in zebrafish. All data were analyzed by *t*-test using GraphPad PRISM 7.00. Analysis of variance was then performed to assess the differences in seizure and latency between experimental groups.

Research results

The three NMDA-administration methods triggered different patterns of the epileptic process in adult zebrafish. Seizure scores were increased after increasing NMDA concentration regardless of the mode of administration. However, the curve of immersion continuously rose to a high plateau (after 50 min), while the curves of intravitreal injection and intraperitoneal injection showed a spike in the early stage (10-20 min) followed by a steady decrease in seizure scores. Furthermore, pretreatment with resveratrol and MK-801 significantly delayed seizure onset time and lowered seizure scores.

Research conclusions

Intravitreal injection of NMDA was the most suitable route for establishing an acute epileptic model in zebrafish, while immersion with NMDA may be an appropriate method for inducing persistent seizures. Additionally, MK-801 and resveratrol showed strong anti-epileptic effects; thus, both of them may be clinically valuable treatments for epilepsy.

Research perspectives

Further study using our models to perform antiepileptic drug screening is necessary, and further work is needed to explore the mechanism of resveratrol against epilepsy.

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SYSTEMATIC REVIEWS

Pimavanserin for the treatment of psychosis in Alzheimer's disease: A literature review

Shilpa Srinivasan, Rajesh R Tampi, Kripa Balaram, Arushi Kapoor

ORCID number: Shilpa Srinivasan 0000-0002-5852-2819; Rajesh R Tampi 0000-0002-0042-8344; Kripa Balaram 0000-0002-1943-7339; Arushi Kapoor 0000-0001-7020-1834.

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Shilpa Srinivasan, Department of Neuropsychiatry and Behavioral Science, Palmetto Health USC Medical Group, University of South Carolina School of Medicine, Columbia, SC 29203, United States

Rajesh R Tampi, Department of Psychiatry and Behavioral Sciences, Cleveland Clinic Akron General, Akron, OH 44307, United States

Rajesh R Tampi, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH 44195, United States

Kripa Balaram, MD, Department of Psychiatry, MetroHealth, Cleveland, OH 44109, United States

Arushi Kapoor, Penn Memory Center at the Penn Neuroscience Center, Perelman Center for Advanced Medicine, Philadelphia, PA 19104, United States

Corresponding author: Shilpa Srinivasan, MD, Doctor, Professor, Department of Neuropsychiatry and Behavioral Science, Palmetto Health USC Medical Group, University of South Carolina School of Medicine, 3555 Harden Street Extension, Suite 301, Columbia, SC 29203, United States. shilpa.srinivasan@uscmed.sc.edu

Abstract

BACKGROUND

Alzheimer's disease (AD) is among the most prevalent forms of dementia in the world and neuropathological studies suggest similar high prevalence of mixed (AD + vascular) dementias. Approximately 25%-50% of individuals with AD develop psychosis sometime during their illness. The presence of psychosis in AD worsens outcomes. Currently there are no United States Food and Drug Administration (FDA) approved medications for the treatment of psychosis in AD. Pimavanserin, a novel atypical antipsychotic medication, was approved by the FDA for the treatment of hallucinations and delusions associated with Parkinson disease psychosis and is currently in clinical trials for the treatment of psychosis in AD.

AIM

To evaluate the existing literature regarding the use of pimavanserin for treating psychosis among individuals with AD.

METHODS

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A literature review of clinical studies of pimavanserin treatment for psychosis in individuals with AD was performed using the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. Trials were identified by systematically searching PubMed, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus through October 2019. The 5-point Jadad scoring system was used to assess the methodologic quality of the randomized placebo-controlled trials.

RESULTS
A total of 499 citations were retrieved and pooled in EndNote and de-duplicated to 258 citations. This set was uploaded to Covidence for screening. Two separate screeners (Srinivasan S and Tampi RR) evaluated the titles, abstracts, and full text of eligible articles. Of the identified 258 abstracts, 98 articles underwent full text review and 2 publications from 1 randomized controlled trial (RCT) were included in the final analysis. The quality of evidence was assessed to be of good methodologic quality, scoring 4 out of 5 using the 5-point Jadad questionnaire with the Jadad Scoring calculation. This systematic review found only one RCT that evaluated the use of pimavanserin for the treatment of psychosis among individuals with AD. This phase 2 trial resulted in two publications, the second of which was a subgroup analysis from the original study. The evidence from these two publications showed that pimavanserin improves psychotic symptoms among individuals with AD when compared to placebo at week 6.

CONCLUSION
Pimavanserin may be a pharmacologic consideration for the treatment for psychosis in AD. Additional RCTs are needed to assess the evidence of effectiveness before pimavanserin is considered a standard treatment.

Key words: Pimavanserin; Alzheimer's disease; Psychosis; Psychotic disorders; Antipsychotic agents

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Core tip: This systematic review was conducted to evaluate the evidence from randomized controlled clinical trials of pimavanserin for the treatment of psychosis in individuals with Alzheimer's disease (AD). Behavioral disturbances including psychosis are prevalent in AD, and have a significant impact on management and outcomes. There are currently no United States Food and Drug Administration approved medications for the management of behavioral disturbance in AD. Based on the findings of our systematic review, pimavanserin, a novel atypical antipsychotic, may be a new pharmacologic consideration for treating psychosis in individuals with AD.

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INTRODUCTION

Alzheimer's disease (AD) is among the most prevalent form of dementia, affecting over two-thirds of the 50 million individuals living with dementia globally[1]. The combination of AD and vascular processes, also known as mixed dementia appears to also have a high prevalence according to neuropathological studies. Furthermore, overlap in clinical presentations can blur the distinction between AD and vascular dementia[2]. While cognitive impairment is a prominent clinical manifestation of AD, behavioral changes, also known as behavioral and psychological symptoms of dementia (BPSD) frequently occur. BPSD can include agitation, aggression, anxiety, depressed mood, apathy, and psychosis (delusions, hallucinations, paranoia)[3]. Between 25%-50% of individuals with AD develop psychosis, with variability in course, duration, and severity of psychotic symptoms[4,5]. The impact of psychosis is

far-reaching, affecting individuals and caregivers and is associated with higher rates of cognitive and functional decline, earlier time to institutionalization, higher treatment mortality, and caregiver burden respectively[6,7].

Available data indicates that psychosis in dementia occurs due to anatomical and biochemical changes within the brain[8]. Dysfunction of the adrenergic and serotonergic systems may also contribute to the behavioral symptoms of dementia[9]. Higher levels of norepinephrine in the substantia nigra and lower levels of serotonin in the presubiculum have been noted among individuals with psychosis in dementia when compared to non-psychotic individuals with dementia[10,11]. Neuropathologic changes that contribute to psychosis include the presence of neuritic plaques and tangles in the frontal and temporal cortices of these individuals[10,12,13]. Metabolic and perfusion imaging studies have demonstrated that psychosis in dementia correlates well with frontal, temporal and parietal lobe dysfunction[14-18]. A study of delusional misidentification symptoms (DMS) among individuals with AD found that individuals with DMS showed increased electroencephalograph delta-power over the right hemisphere and their computed tomography scans showed more severe right frontal lobe atrophy, and the number of their pyramidal cells in area CA1 was lower than in the patients without DMS[19]. There is also growing evidence that psychosis among individuals is higher among individuals who have relatives with AD and psychosis[20,21]. Psychosis is also more common among individuals with APOE3/4 genotype with more than threefold increase in the signs of depression and psychosis when compared with individuals with APOE 3/3 genotype or to control subjects[22]. Data also indicates that 5-HT2A receptor polymorphism 102-T/C and the 5-HT2C receptor polymorphism Cys23Ser are associated with the development of visual and auditory hallucinations among individuals with AD[23,24]. A study examining the association between selected polymorphisms in the dopamine receptor genes DRD1, DRD2, DRD3 and DRD4 and the presence of psychosis or aggressive behavior among individuals with AD found that psychosis and aggression were both significantly more frequent among the DRD1 B2/B2 homozygotes ($P < 0.02$), while psychosis was significantly more frequent in DRD3 1/1 or 2/2 homozygotes ($P < 0.05$)[25]. Another study found an association between the presence of psychotic symptoms and aggressive behavior and the DRD1 polymorphism and between the presence of psychosis, but not aggression and the DRD3 polymorphism[26]. Carriers of the DRD1 B2 allele were more likely to be aggressive or experience hallucinations whereas homozygous carriers of the DRD3 1 allele were more likely to experience delusions. These studies indicate that BPSD develops as a byproduct of the neurodegenerative disease process that manifests after a certain period, when the genetic factors assume greater significance in the brain[8].

Although non-pharmacological interventions are considered first line for BPSD, pharmacologic interventions may be warranted particularly when psychotic symptoms pose a potential threat to the individual or caregivers[27,28]. In the United States, there are currently no Federal Drug Administration (FDA)- approved medications for the treatment of psychosis in AD. While antipsychotic medications have been used to treat BPSD in individuals with AD, efficacy rates from randomized clinical trials have been shown to be modest[29,30]. In a systematic review conducted by Tampi *et al*[30] of 16 published meta-analyses evaluating antipsychotics in individuals with dementia, antipsychotics (convention and second generation/atypical) were found to demonstrate modest efficacy for the treatment of psychosis, agitation and aggression. However, significant limitations from an adverse effect profile were notable. The safety profile of antipsychotic medications must be considered, as they are associated with increased risk for death, cerebrovascular adverse events, sedation, falls, and pneumonia[29-32]. With these significant safety risk concerns, warnings regarding the use of antipsychotics in individuals with dementia-related psychosis have been issued by the United States FDA, the European Medicines Agency, and the United Kingdom Medicines and Healthcare Products Regulatory Agency[32]. Other pharmacologic agents, including cognitive enhancers (acetylcholinesterase inhibitors, memantine), glutamate modulators (dextromethorphan/quinidine), antidepressants and hormonal agents have been studied for agitation and aggression in AD with varying results and limited utility[7]. However, off-label use of antipsychotics, for dementia-related psychosis continues across different healthcare settings[33,34]. As a result, effective and safe pharmacological treatment of psychosis in AD remains an ongoing need.

Pimavanserin, an atypical antipsychotic medication, is a novel selective 5-HT2A inverse agonist with a low affinity for 5-HT2C receptors. Pimavanserin does not demonstrate clinically significant affinity to dopaminergic, histaminergic, muscarinic, or adrenergic receptors[35]. Subsequent to the results of a placebo-controlled six-week

clinical trial, pimavanserin received FDA approval in 2016 for the treatment of hallucinations and delusions associated with Parkinson disease psychosis (PDP)[36,37].

There is emerging evidence that pimavanserin is being trialed for the treatment of dementia-related psychosis[37]. Although published reviews have examined the benefits and risks of antipsychotics for the treatment of psychosis in dementia, to our knowledge, this is the first review that systematically evaluates the evidence from literature on the use of pimavanserin for psychosis in AD from randomized controlled trials (RCTs). In accordance with PICOS format (participants, interventions, comparisons, outcomes, and study design), all identified studies of RCTs in adult patients with AD who received pimavanserin for the treatment of psychosis in AD were included.

MATERIALS AND METHODS

A systematic literature search of clinical trials of pimavanserin was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines[38]. Our study protocol was registered in the PROSPERO database of systematic reviews[39]. All identified studies of RCTs in adult patients with AD who received pimavanserin for the treatment of psychosis in AD were included. Studies of pimavanserin for the treatment of schizophrenia, dementia due to other etiologies, PDP, mood disorders, or other conditions were excluded. Literature involving nonhuman studies was also excluded.

We began our search with the Yale MeSH Analyzer (mesh.med.yale.edu), using key articles to refine the search strategy for the term pimavanserin. In each database we ran scoping queries followed by iterative refinement of the search strategy. Additional articles were identified by examining other systematic reviews, bibliographies, and pre-identified websites such as clinicaltrials.gov and publicly available internet searches (Google Scholar).

Literature searches were performed in the following databases from inception to October 25, 2019: PubMed, MEDLINE (Ovid), EMBASE (Ovid), Cochrane Central Register of Controlled Trials (Wiley), Web of Science Core Collection (Clarivate), and Scopus (Elsevier). No date or language restrictions were applied.

The databases were searched using both controlled vocabulary words and synonymous free text words for pimavanserin. The Cochrane highly sensitive search strategy was used to identify randomized trials in PubMed and Ovid databases[40]. The Cochrane RCT search strategy was adapted to identify trials in other electronic databases[41]. The search strategies were adjusted for the syntax appropriate for each database/platform. See supplementary material for MEDLINE search strategy (Supplementary Material).

RESULTS

The search retrieved a total of 499 references, which were pooled in EndNote and de-duplicated. This set was uploaded to Covidence for screening, which identified additional duplicates, leaving 258 for screening[42]. Two separate screeners (Srinivasan S and Tampi RR) evaluated the titles, abstracts, and full text of eligible articles. Of the identified 258 abstracts, 98 articles underwent full text review (Figure 1).

A total of two publications of pimavanserin among individuals with psychosis due to AD were identified and reviewed. Both were rated as being of good methodologic quality based on the five-point Jadad Score calculation[43]. This calculation assigns two points for randomization (one point for randomization and one point for description of system used to generate sequence of randomization), two points for blinding (description of, and method of blinding), and one point for description of withdrawals (Table 1). There was no funding for this review.

We identified and reviewed a total of two publications of pimavanserin for the treatment of psychosis in individuals with AD from a single trial. The trial used the aforementioned Jadad score calculation and was rated as being of good methodological quality (score of 4/5). The publications are described individually below and a brief summary of both publications is outlined in Table 2.

Study from Ballard et al, 2018

The 2018 study by Ballard *et al*[44] was a phase 2, randomized, double-blind, placebo-

Table 1 Jadad questionnaire

Jadad score calculation	
Item	Score (Yes = 1)
Was the study described as randomized	0/1
Was the method used to generate sequence of randomization described and appropriate?	0/1
Was the study described as double-blind?	0/1
Was the method of blinding described and appropriate?	0/1
Was there a description of withdrawals and dropouts?	0/1

Table 2 Summary of publications

Ref.	Year	Number of participants	Age (yr)	Setting	Comparators	Duration
Ballard *et al*[44]	2018	181 (pimavanserin n = 90; placebo n = 91)	≥ 50	Nursing homes	17 mg × 2 tablets pimavanserin *vs* placebo (2 tablets)	12 wk
Ballard *et al*[45]	2019	181 (pimavanserin n = 90; placebo n = 91)	≥ 50	Nursing homes	34 mg pimavanserin *vs* placebo	12 wk

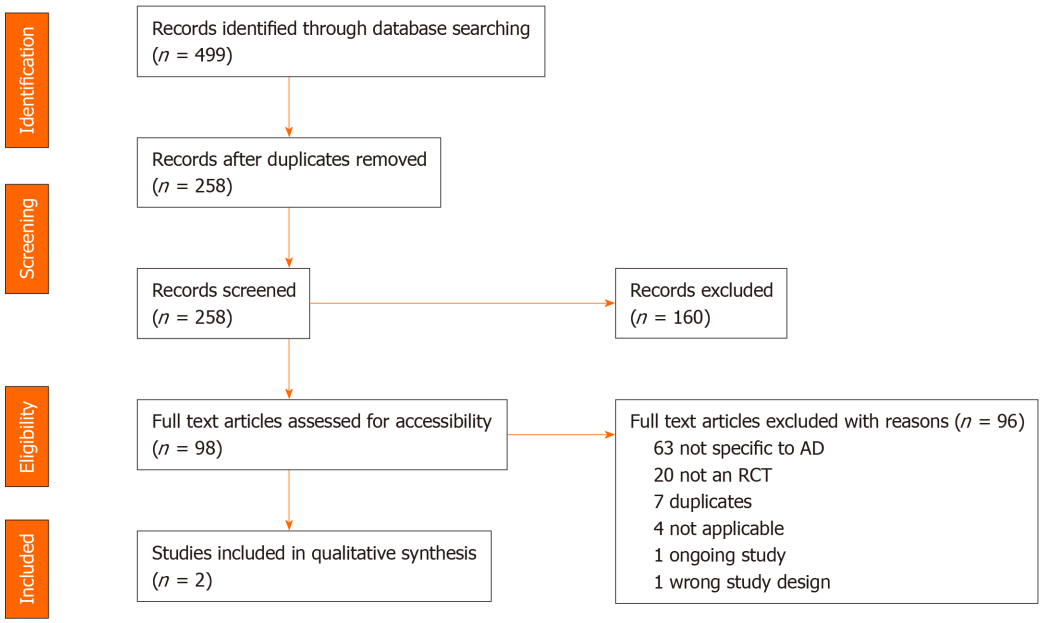


Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram. AD: Alzheimer's disease; RCT: Randomized controlled trial.

controlled single center trial. This study was conducted at nursing homes across the United Kingdom. Pimavanserin was compared to placebo in individuals with possible or probable AD and psychotic symptoms (visual or auditory hallucinations, delusions or both). This trial was 12 wk in duration and participants were aged 50 years or older. After completing screening and baseline evaluations, trial participants were randomly assigned in a 1:1 ratio to receive either pimavanserin or placebo. Pimavanserin dosing was two 17 mg tablets daily and placebo was also dosed as two tablets daily. Participants had to have resided in the nursing home for at least 4 wk in order to be eligible for the study. The degree of psychotic symptoms meeting eligibility criteria included clinical severity warranting antipsychotic treatment, and participant score of ≥ 4 for frequency × severity of hallucinations or delusions domains of the Neuropsychiatric Inventory-Nursing Home version (NPI-NH) psychosis scale, or a total combined score of ≥ 6 for hallucinations and delusions. Groups were stratified

based on baseline Mini-Mental State Examination (MMSE) total score of ≤ 6 or ≥ 6, and NPI-NH psychosis score of ≤ 12 or ≥ 12. Following screening, brief psychosocial therapy therapists evaluated participants during a 3-wk period and only individuals determined to require pharmacologic intervention progressed to study randomization, in an effort to minimize placebo response. This 3-wk period also served as a washout phase for participants who were taking antipsychotic medications.

After progressing through screening, individuals who m *et al*l study eligibility criteria at baseline (day 1) received a single dose of either pimavanserin (two 17 mg tablets) or placebo (two tablets). Participants continued to receive this regimen daily for 12 wk. Study visits were conducted at 2-wk intervals following baseline (day 1): days 15, 29, 43, 64, and 85, or at early termination. A telephone follow-up visit after the last dose of study medication was conducted for safety.

The primary outcome of this study was efficacy of pimavanserin *vs* placebo based on a change from baseline to week 6 in the NPI-NH psychosis score (hallucinations + delusions). Additional correlation analyses at week 6 included NPI-NH total score, NPI-NH agitation/aggression. AD Cooperative Study- Clinical Global Impression of Change (ADCS-CGIC), AD Cooperative Study- Activities of Daily Living (ADCS-ADL) total score, and the Cohen-Mansfield Agitation Inventory- Short Form (CMAI-SF) total score[45-48]. The assessment of behavioral symptoms at 6 wk and 12 wk constituted the secondary outcomes assessment. The ADCS-CGIC, NPI-NH agitation/aggression and sleep and nighttime domains, and the CMAI-SF total and subdomain scores were used as a measure of agitation. Additional subgroup analyses focused on stratified NPI- NH scores (< 12 or ≥ 12), baseline MMSE (< 6 or ≥ 6), sex, age (≤ 85 years or > 85 years). As well as for concomitant use of anti-dementia medication, selective serotonin reuptake inhibitor, and previous antipsychotic use. The MMSE was used to assess cognitive impairment, and the 1987 Unified Parkinson's Disease Rating Scale (UPDRS) Part III was used to measure extrapyramidal symptoms[49,50].

All study participants who received pimavanserin or placebo were included in the safety analysis, with safety outcomes measured over 12 wk. An adverse event checklist (all reported adverse events, those leading to study discontinuation, serious adverse events, and mortality), physical examinations, vital signs and electrocardiogram, and laboratory tests were also conducted.

Out of 345 screened participants, 181 were randomized to receive pimavanserin (n = 90) *vs* placebo (n = 91). Three participants in the pimavanserin group did not have a post-baseline NPI-NH score, and were excluded from the analysis. Of the 178 participants who were included, 160 completed 6 wk of treatment and 140 completed 12 wk. Of 26% of participants (n = 23) in the pimavanserin group and 20% of those (n = 18) in the placebo group withdrew over the 12-wk study period. The mean MMSE score was 10.3 in the pimavanserin group and 9.8 in the placebo group.

More women (80%-82%) than men and white individuals were represented among study participants. The mean age (years) in both groups was balanced (85.6 years in the pimavanserin group and 86.1 years in the placebo group). More study participants had an NPI-NH psychosis score < 12 (60%-61%). The mean MMSE score was 10.3 in the pimavanserin group and 9.8 in the placebo group.

The investigators noted that the improvement in the primary outcome (change in NPI-NH psychosis score) at week 6 was higher in the pimavanserin group (39.5% reduction) *vs* the placebo group (19.3% reduction). They did not observe any statistically significant differences between pimavanserin and placebo for the additional correlational analyses at week 6 or at week 12. Although not statistically significant (P = 0.063), a numerical difference of 5 points in the NPI-NH total score was observed for pimavanserin compared with placebo at week 6.

In regard to discontinuation due to adverse events, the investigators reported a 9% dropout rate (n = 8 of 90) in the pimavanserin group and 12% (n = 11 of 91) in the placebo group. Falls, urinary tract infection, and agitation were the most common adverse events across both treatment groups. While the frequency of falls (23%) and urinary tract infections (22% *vs* 28%) were similar across both treatment groups, more participants receiving pimavanserin experienced agitation compared to placebo. Agitation (21% *vs* 14%), aggression (10% *vs* 4%), and peripheral edema (8% *vs* 2%) were more prevalent in the pimavanserin treated group than with placebo. The investigators also did not note differences in vital signs, clinical laboratory results or physical examinations between groups. There were no discontinuations due to QTc prolongation. Furthermore, the investigators found no evidence of decline in cognition, function, global outcome, or motor symptoms over the 12-wk study period.

A summary of the findings from the 2018 Ballard *et al*[44] study, adverse events, and strengths/limitations are included in Table 3.

Table 3 Summary Ballard *et al*[44], 2018

Ref.	Outcomes	Tolerability	Limitations
Ballard *et al*[44], 2018	**Primary outcome**: **At week 6:** (1) Significant improvement in NPI-NH psychosis score (mean change was -3.76 points (SE 0.65) for pimavanserin group and -1.93 points (0.63) for placebo (mean difference -1.84 [95%CI: -3.64, -0.04]; P = 0.045) without negative effects on cognition or motor function; (2) Response (≥ 30% improvement) in 55% (pimavanserin) *vs* 37% (placebo); and (3) In NPI-NH < 12 subgroup: Mean change of the score from baseline to week 6 was -0.58 (95%CI: -2.10, 0.95) for pimavanserin *vs* -0.16 (-1.60 to 1.28) for placebo [mean difference -0.42 (95%CI: -2.52, 1.68)], Cohen's d = –0.77; P = 0.694. **At week 12:** No significant advantage for pimavanserin *vs* placebo was observed for the overall study population [treatment difference -0.51 (95%CI: -2.23, 1.21); P = 0.561]. **Secondary outcome: At weeks 6 and 12**: No significant differences between placebo and pimavanserin for ADCS–CGIC, NPI–NH agitation/aggression, NPI–NH sleep and nighttime behavior disorders, and CMAI–SF	Adverse events (pimavanserin *vs* placebo). **Most common:** (1) Agitation (21% *vs* 14%); (2) Aggression (10% *vs* 4%); (3) Falls (21% *vs* 21%); (4) Urinary tract infection (20% *vs* 25%); and (5) Peripheral edema (8% *vs* 2%). **Less common:** (1) Weight loss (-0.7 kg *vs* -0.1 kg); (2) QTc prolongation (9.4 ms *vs* -0.2 ms); and (3) Death (4 *vs* 4)	**Limitations:** (1) Study was not sufficiently powered to control for secondary outcomes; (2) Limited number of participants in severe psychosis subcategory or prior history of antipsychotic use; (3) Biomarker confirmation for patients diagnosed with Alzheimer's was not possible in the nursing home patients; (4) Possibility of trial participants inclusion of non-Alzheimer's type and mixed dementia; (5) High attrition rate: 26% (pimavanserin) and 20% (placebo); and (6) Absence of active comparator to assess efficacy/tolerability between pimavanserin and other antipsychotics. **Strengths**: (1) Rigorous diagnosis of psychosis – high completion rate at week 12; (2) Participants assessed in the community care homes providing access to the elderly population to be included in the clinical study; and (3) Researchers were able to study frail, elderly participants in their "natural" environment

CI: Confidence interval; NPI–NH: Neuropsychiatric Inventory-Nursing Home version; CMAI–SF: Cohen-Mansfield Agitation Inventory- Short Form; ADCS–CGIC: Alzheimer's disease Cooperative Study- Clinical Global Impression of Change.

Study from Ballard et al, 2019

This paper describes the outcomes of efficacy and tolerability of pimavanserin *vs* placebo in a subgroup of patients with severe psychosis associated with AD. Participants were part of the Phase 2 study summarized above and reported by Ballard *et al*[44] in 2018. The severity of psychosis was quantified by a cut-off score of ≥ 12 on the NPI-NH psychosis score. Participants in this subgroup analysis were nursing home residents with a baseline NPI-NH-NS score of ≥ 12, who were randomized to receive pimavanserin 34 mg or placebo daily over a 12-wk period. The primary endpoint at week 6 was the mean change from baseline on the NPI-NH-PS score. In addition, the investigators performed responder analyses, which was described as the observed proportions of individuals with an improvement from baseline at week 6. The investigators ascribed any missing values as non-responders.

The subgroup comprised of 57 participants (pimavanserin n = 27; placebo n = 30). Over 80% of participants in both pimavanserin and placebo groups were women. The average age range of participants was 85 years. A minority of participants in both groups had prior antipsychotic treatment (11.1% and 13.1%, pimavanserin *vs* placebo respectively). MMSE scores were similar across both pimavanserin and placebo subgroups (8.6 and 9.2 respectively) but were lower than in the overall study population described in the previous section.

In this subgroup, mean baseline NPI-NH psychosis scores were 15.3 (pimavanserin group) and 16.7 (placebo group). There was a statistically significant change in NPI-NH psychosis scores for pimavanserin *vs* placebo. Furthermore, the investigators reported that of 81% of study participants who had both hallucinations and delusions at baseline, pimavanserin was superior to placebo in treating these symptoms, with statistically significant improvement noted at week 6 for both domain scores (P = 0.046

for NPI-NH hallucinations, and P = 0.034 for NPI-NH delusions). While two-thirds of pimavanserin treated study participants had improvements in their NPI-NH psychosis score to < 6 (*vs* 32 % of placebo treated individuals) at week 6, 45.5% of both groups demonstrated this drop in NPI-NH score at week 12.

From a tolerability standpoint, there were no significant differences in the incidence of adverse events in the subgroup compared to the study population overall. Agitation, urinary tract infections and falls were the most common adverse events in the pimavanserin treated cohort. Over the 12-wk study period, the investigators noted that the change in MMSE score from baseline for the overall population across both treatment groups was minimal.

A summary of the findings from the 2019 Ballard *et al*[45] subgroup analysis, adverse events, and strengths/limitations are included in Table 4.

DISCUSSION

This review indicates that there is only one RCT that evaluated the use of pimavanserin for the treatment of psychosis among individuals with AD. This phase 2 trial resulted in two publications, the second of which was a subgroup analysis from the original study. The RCT was rated as having good methodological quality, scoring 4/5 on the Jadad score calculation. The evidence from these two publications indicates that pimavanserin improves psychotic symptoms among individuals with AD when compared to placebo at week 6. Additionally, among individuals with more severe psychotic symptoms (NPI-NH-NS score of ≥ 12), those individuals who were treated with pimavanserin had better outcomes than individuals receiving placebo. Pimavanserin was well tolerated in the study with the discontinuation rate due to adverse events being 9% in the pimavanserin group *vs* 12% in the placebo group. The investigators reported falls, urinary tract infection and agitation as the most common adverse events across both treatment groups with the frequency of falls (23%) and urinary tract infections (22% *vs* 28%) being similar across the treatment groups. Agitation (21% *vs* 14%), aggression (10% *vs* 4%) and peripheral edema (8% *vs* 2%) were more prevalent in the pimavanserin group when compared to placebo. The investigators also did not note any differences in vital signs, clinical laboratory results or physical examinations between the two groups. There were no discontinuations due to QTc prolongation. Additionally, treatment with pimavanserin did not result in decline in cognition, function, global outcome or motor symptoms over the 12-wk study period.

The strength of this review was the extensive review of multiple databases without any language restrictions. The limitation was that we restricted our review to only RCTs on the use of pimavanserin for the treatment of psychosis among individuals with AD. A review of clinicaltrials.gov found the SERENE study, conducted between 2016-2018 to evaluate the efficacy of pimavanserin 20 mg and 34 mg) *vs* placebo in the treatment of agitation and aggression in individuals with AD over 12 wk[51]. The primary outcome measure was change in the Cohen-Mansfield Agitation Inventory, while the secondary outcome measure was the Zarit Burden Interview, a measure of dementia caregiver stress[52]. While the original study design aimed to recruit 432 participants, 111 were randomized before recruitment was halted for business reasons. The investigators noted that the final study with 111 participants was no longer sufficiently powered to detect treatment effect.

Our review only found one RCT that met our inclusion criteria. The limitations of the study that we included in review were as follows: It was not sufficiently powered to control for secondary outcomes, there were limited number of participants in the severe psychosis subcategory or with a prior history of antipsychotic use, there were no biomarker confirmation for individuals with a diagnosis of AD who were living in the nursing homes and a high attrition rate among the pimavanserin (26%) and placebo (20%) groups. There strengths of the study were that there was a stringent criteria for the diagnosis of psychosis and there was participation from frail older adults living in community care homes in the study.

In a meta-analysis, Yasue *et al*[53] found that pimavanserin reduced the symptoms of hallucinations and delusions when compared to placebo [weighted mean differences (WMD) = -2.26, P = 0.005] among individuals with PDP. Additionally, pimavanserin was found to be superior to placebo in improving symptoms of hallucinations (WMD = -2.15, P = 0.001) and delusions (WMD = -1.32, P = 0.010) when considered independently. The authors did not find any significant difference between pimavanserin and placebo on the all-cause discontinuation rates for adverse events,

Table 4 Summary Ballard *et al*[45], 2019

Ref.	Outcomes	Tolerability	Limitations
Ballard *et al*[45], 2019	For overall population: Adjusted mean change from baseline at week 6 (adjusted mean, MMRM analysis) for the NPI-NH psychosis score was -3.76 (0.65) for pimavanserin *vs* -1.93 (0.63) for placebo (delta = -1.84, 95% confidence interval (CI) [-3.64, -0.04], Cohen's d = -0.32, P = 0.045); For patients with NPI-NH scores > 12: The mean change at week 6 was -10.15 (95%CI: -12.50, -7.80) for pimavanserin *vs* -5.72 (95%CI: -8.14, -3.30) for placebo (delta = -4.43 (95%CI: -7.81, -1.04), Cohen's d effect size of -0.73, P = 0.011); In the more severe subgroup, pimavanserin was superior to placebo at week 6 in treating both hallucinations (P = 0.046) and delusions (P = 0.034); At week 6, 66.7% of those in the pimavanserin group improved to an NPI-NH psychosis score < 6 *vs* 32.0% of those in the placebo group (difference = 34.7%); At week 12, 45.5% of both pimavanserin and placebo-treated patients had an NPI-NH psychosis score < 6; The proportion with a baseline NPI-NH psychosis score ≥ 12 achieving a response was significantly (P < 0.05) greater with pimavanserin *vs* placebo	Incidence of aggression was 14.3% in the severe psychosis subgroup *vs* 10.0% in overall population; Incidence of agitation was 17.9% in severe subgroup and 21.1% in general population; Other side effects included falls, UTI, contusion, respiratory tract infections, anemia, edema, cellulitis, anxiety, increase in urea or potassium	Small sample size in subgroup; Subgroup analysis was secondary
1	1	1	1

CI: Confidence interval; NPI–NH: Neuropsychiatric Inventory-Nursing Home version; UTI: Urinary tract infections.

death, Parkinson motor symptoms and the incidence of individual adverse events. Additionally, pimavanserin was found to be associated with less orthostatic hypotension when compared to placebo (risk ratio = 0.33, P = 0.008, number needed to harm = 17, P = 0.01). The investigators concluded that pimavanserin is beneficial for the treatment of symptoms of PDP and is well tolerated.

The data published by Institute for Safe Medication Practices indicated that there were a total 2236 adverse events reported from the use of pimavanserin in the 12 mo post-marketing observation period that ended March 2017, with hallucinations 487 (21.8%) drug ineffectiveness 333 (14.9%), confused state 258 (11.5%) and death 244 (10.9%) being the most commonly adverse events[54]. The United States FDA post-marketing review did not identify any new or unexpected safety findings with the use of pimavanserin[55]. In addition, the FDA did not find information that was inconsistent with the established safety profile for the drug concluding that the drug's benefits outweigh its risks among individuals with PDP reporting hallucinations and delusions.

In conclusion, the data is limited given only one published RCT to date has examined the use of pimavanserin for the treatment of psychosis among individuals with AD. While evidence from this study suggests pimavanserin is effective and tolerated, more rigorous trials are needed to establish evidence of effectiveness. However, given the identified risks of using antipsychotics among individuals with dementia, caution should be advised when using newer antipsychotic medications among individuals with dementia[56]. Additional larger studies of longer duration of treatment with positive outcomes will be needed prior to pimavanserin being adopted as a standard treatment option among individuals with AD who have psychosis.

ARTICLE HIGHLIGHTS

Research background

Alzheimer's disease (AD) is among the most prevalent forms of dementia in the world. Approximately 25%-50% of individuals with AD develop psychosis sometime during their illness. The presence of psychosis in AD worsens outcomes. Currently there are no United States Food and Drug Administration (FDA) approved medications for the treatment of psychosis in AD.

Research motivation

Pimavanserin, a novel atypical antipsychotic medication, was approved by the FDA for the treatment of hallucinations and delusions associated with Parkinson disease psychosis and is currently in clinical trials for the treatment of psychosis in AD.

Research objectives

This review evaluates the existing literature regarding the use of pimavanserin to treat psychosis among individuals with AD.

Research methods

A literature review of clinical studies of pimavanserin treatment for psychosis in individuals with AD was performed using the preferred reporting items for systematic review and meta-analysis guidelines. Trials were identified by systematically searching PubMed, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus through October 2019. The 5-point Jadad scoring system was used to assess the methodologic quality of the randomized placebo-controlled trials.

Research results

This systematic review found only one randomized controlled trial (RCT) that evaluated the use of pimavanserin for the treatment of psychosis among individuals with AD. This phase 2 trial resulted in two publications, the second of which was a subgroup analysis from the original study. The evidence from these two publications showed that pimavanserin improves psychotic symptoms among individuals with AD when compared to placebo at week 6.

Research conclusions

Limited evidence indicates that pimavanserin may be a pharmacologic consideration for the treatment for psychosis in AD. Additional RCTs are needed to assess the evidence of effectiveness before pimavanserin is considered a standard treatment.

Research perspectives

Additional RCTs are needed to assess the evidence of effectiveness before pimavanserin would be considered a standard treatment for psychosis in AD.

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ABOUT COVER

Editorial board member of *World Journal of Psychiatry*, Dr. Wang is an Associate Researcher at the School of Medicine, São Paulo University in São Paulo, Brazil. Having received his MD degree from the same institution in 1987, Dr. Wang commenced postgraduate training in the university's Department of Psychiatry, receiving his Master's degree in 1995 and PhD in 2003. Since 2007, he has mentored Master's and PhD students in the Department of Psychiatry and been involved in population-based epidemiological surveys on mental health at the Section of Psychiatric Epidemiology (LIM-23). Since 2016, he has been a collaborator of the Global Burden of Disease Initiative, under the auspice of Washington University in Seattle, WA, United States. His ongoing research interests involve the application of evidence-based medicine in mental health, particularly in association with non-communicable diseases. (L-Editor: Filipodia)

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ORIGINAL ARTICLE

Basic Study

Serum levels of chemokines in adolescents with major depression treated with fluoxetine

Francisco Rafael de la Peña, Carlos Cruz-Fuentes, Lino Palacios, Manuel Iván Girón-Pérez, Emilio Medina-Rivero, Maria Dolores Ponce-Regalado, Samantha Alvarez-Herrera, Gilberto Pérez-Sánchez, Enrique Becerril-Villanueva, José Luis Maldonado-García, María C Jiménez-Martínez, Lenin Pavón

ORCID number: Francisco Rafael de la Peña 0000-0001-5421-2744; Carlos Cruz-Fuentes 0000-0001-9586-4052; Lino Palacios 0000-0001-9533-2996; Manuel Iván Girón-Pérez 0000-0001-6808-6590; Emilio Medina-Rivero 0000-0001-8862-1378; Maria Dolores Ponce-Regalado 0000-0002-3477-1861; Samantha Alvarez-Herrera 0000-0001-9747-885X; Gilberto Pérez-Sánchez 0000-0003-3878-0631; Enrique Becerril-Villanueva 0000-0001-7210-9775; José Luis Maldonado-García 0000-0003-2694-1290; María C Jiménez-Martínez 0000-0003-3982-9097; Lenin Pavón 0000-0002-6067-6868.

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Francisco Rafael de la Peña, Lino Palacios, Adolescent Clinic, Clinical Services, National Institute of Psychiatry, "Ramón de la Fuente", Mexico City 14370, Mexico

Carlos Cruz-Fuentes, Department of Psychiatric Genetics, Clinical Research Branch, National Institute of Psychiatry, "Ramón de la Fuente", Mexico City 14370, Mexico

Manuel Iván Girón-Pérez, Universidad Autónoma de Nayarit, Laboratorio de Inmunotoxicología, Boulevard Tepic-Xalisco s/n, Cd de la Cultura Amado Nervo, Tepic 63000, Mexico

Manuel Iván Girón-Pérez, Centro Nayarita de Innovación y Transferencia de Tecnología A.C. Laboratorio Nacional para la Investigación en Inocuidad Alimentaria-Unidad Nayarit, Calle Tres s/n. Cd Industrial, Tepic 63000, Nayarit, Mexico

Emilio Medina-Rivero, Unidad de Desarrollo e Investigación en Bioprocesos, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Unidad Profesional Lázaro Cárdenas, Mexico City 11340, Mexico

Maria Dolores Ponce-Regalado, Departamento de Ciencias de Salud, Centro Universitario de los Altos, Universidad de Guadalajara Av Rafael Casillas Aceves No.1200, Tepatitlán de Morelos, Jalisco, 47610, Mexico

Samantha Alvarez-Herrera, Gilberto Pérez-Sánchez, Enrique Becerril-Villanueva, José Luis Maldonado-García, Lenin Pavón, Laboratory of Psychoimmunology, National Institute of Psychiatry, "Ramón de la Fuente", Mexico City 14370, Mexico

María C Jiménez-Martínez, Department of Immunology and Research Unit, Institute of Ophthalmology "Conde de Valenciana Foundation", Mexico City 06800, Mexico

María C Jiménez-Martínez, Department of Biochemistry, Faculty of Medicine, National Autonomous University of Mexico, Mexico City 04510, Mexico

Corresponding author: Lenin Pavón, PhD, Professor, Laboratory of Psychoimmunology, National Institute of Psychiatry, "Ramón de la Fuente", Calzada México-Xochimilco 101, Colonia San Lorenzo Huipulco, Mexico City 14370, Mexico. lkuriaki@imp.edu.mx

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Abstract

BACKGROUND

Major depressive disorder (MDD) is a global health issue that affects 350 million people of all ages. Although between 2% and 5.6% of affected individuals are adolescents, research on young patients is limited. The inflammatory response contributes to the onset of depression, and in adult MDD patients, symptom severity has been linked to chemokine levels.

AIM

To determine the differences in circulatory levels of chemokines in healthy volunteers (HVs) and adolescents with MDD, and assess the changes induced by fluoxetine consume.

METHODS

The 22 adolescents with MDD were monitored during the first 8 wk of clinical follow-up and clinical psychiatric evaluation was done using the Hamilton depresión rating scale (HDRS). The serum levels of monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1α, MIP-1β, interleukin (IL)-8, interferon gamma-induced protein (IP)-10, and eotaxin were measured in patients and HVs.

RESULTS

In all cases, significant differences were detected in circulating chemokine levels between patients before treatment and HVs ($P < 0.0001$). All chemokines decreased at 4 wk, but only MCP-1 and IL-8 significantly differed ($P < 0.05$) between 0 wk and 4 wk. In the patients, all chemokines rose to their initial concentrations by 8 wk *vs* 0 wk, but only IP-10 did so significantly ($P < 0.05$). All patients experienced a significant decrease in HDRS scores at 4 wk ($P < 0.0001$) and 8 wk ($P < 0.0001$) compared with 0 wk.

CONCLUSION

Despite the consumption of fluoxetine, patients had significantly higher chemokine levels, even after considering the improvement in HDRS score. The high levels of eotaxin, IP-10, and IL-8 partially explain certain aspects that are affected in MDD such as cognition, memory, and learning.

Key words: Adolescents; Major depression; Chemokine; Fluoxetine; Interferon gamma-induced protein-10

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Core tip: Major depressive disorder affects 350 million persons, of whom approximately 6% are adolescents. This study determined the differences in circulatory levels of chemokines including eotaxin, interleukin-8, induced protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and macrophage inflammatory protein-1β in healthy volunteers and adolescents with major depression. In addition, the changes induced by antidepressants consumed during 8 wk of clinical follow-up were assessed, which is the minimum time to observe the therapeutic efficacy of selective serotonin reuptake inhibitors, such as fluoxetine in adolescents. Our results showed significant elevation in serum chemokine levels in adolescents with major depression despite treatment with fluoxetine, and an improvement in scores on the Hamilton depresión rating scale.

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INTRODUCTION

Major depressive disorder (MDD) is a significant international health problem affecting 350 million people of all ages globally[1]. Studies worldwide have reported prevalence rates of depression between 2.8% and 5.6% in adolescents[2], yet research on this clinical condition is limited. The depressive symptomatology in adolescents can be confused with other psychiatric disorders, in turn affecting the proper diagnosis and normal development of patients. MDD in adolescents is associated with several negative outcomes including other psychiatric disorders later in life, educational impairment, self-injury, and suicide[2,3].

The inflammatory response contributes to the onset of depression, as demonstrated by several meta-analyses[4,5]. Three pathways interacting with the central nervous system (CNS) have been described through the peripheral inflammatory response[6,7]. The first are the inflammatory factors that directly diffuse into the brain through leakage of the blood-brain barrier; the second pathway is when circulatory inflammatory factors indirectly act to stimulate the secretion of central inflammatory factors through vagal afferent nerves; the last pathway is when CNS cells directly produce inflammatory molecules and express their receptors. The first two possible ways help explain that the peripheral administration of cytokines can produce depressive-like symptoms, while the third way suggests that high levels of cytokines in the CNS may be strongly associated with the development of MDD, and that the circulatory cytokines levels correlate with cytokine levels in the CNS[8].

These findings have prompted interest in soluble inflammatory molecules, called chemokines[9]. Chemokines are considered a subtype of cytokines based on their functions during inflammation, although they differ structurally from cytokines. Canonically, chemokines favor the migration of leukocytes towards inflamed tissues along a concentration gradient, modulating cellular inflammatory responses[10]. In addition, clinical evidence has demonstrated that chemokines are produced by astrocytes, microglia, and neurons[11]. Chemokines and their receptors have significant functions in the CNS, for example, in brain development, plasticity, cell-to-cell communication, neurotransmission, neuroendocrinology, inflammatory processes, and behavioral regulation[9,12].

A wide range of chemokines have been implicated in the develop of depression and depression-like behavior[9,12-15]. Vogelzangs *et al*[16] reported an association between interleukin (IL)-8, monocyte chemoattractant protein-1 (MCP-1), and matrix metalloproteinase-2 serum levels and depressive symptom severity in 591 patients. Nevertheless, few studies have evaluated serum chemokine levels in adolescents with MDD before and during clinical follow-up. Therefore, these inflammatory molecules have been proposed to be biological markers of MDD by several groups[17,18].

The objective of this work was to determine the differences in circulatory levels of eotaxin or C-C motif chemokine ligand 11 (CCL11), IL-8 or C-X-C motif chemokine ligand 8 (CXCL8), IP-10 or CXCL10, MCP-1 or CCL2, macrophage inflammatory protein (MIP)-1α or CCL3, and MIP-1β or CCL4 in healthy volunteers (HVs) and adolescents with MDD; and to assess the changes induced by antidepressants consumed during 8 wk of clinical follow-up, which is the minimum time to observe the therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs), as fluoxetine, in adolescents[19].

MATERIALS AND METHODS

Participants

Patients: The Adolescent Clinic of Instituto Nacional de Psiquiatría "Ramón de Fuente," Mexico City, assessed 337 individuals and recruited 22 Mexican patients who met the inclusion criteria from January 2006 to December 2008. The patients were men and women aged 14 to 19 years, who met the diagnostic criteria for MDD per the Diagnostic and Statistical Manual of Mental Disorders IV - text revision, and whose episodes at the moment of the study were moderate. They had no history of treatment for MDD with SSRIs, the duration of their depressive episodes was no longer than 2 years, and their minimum baseline score on the Hamilton depresión rating scale (HDRS) was ≥ 14.

All included participants received an explanation and signed informed consent forms to participate in this study (INPRF-2035). They were recruited per the clinical follow-up in the INPRF-2035 research protocol, as approved by the ethics committee of Instituto Nacional de Psiquiatría, "Ramón de la Fuente Muñiz" Mexico.

Healthy volunteers: Eighteen HVs were recruited from the general population between January 2006 and December 2008. Clinical parameters of HVs were within normal reference ranges (data not shown). The Mini International Neuropsychiatric Interview confirmed that HVs did not suffer from any mental disorder, and all had been free of any medication use by 3 wk before blood sampling. Demographic data of this group are shown in Table 1.

Clinical procedures

Psychiatrists diagnosed all subjects, and the clinical status of adolescents with MDD was determined using the validated Spanish version of the 21-item HDRS-21. Patients were free of antidepressants by 3 wk before the study and signed written consent forms only after receiving a detailed explanation of the study aims. All participants were treated with SSRIs. At the screening visit, after being administered the HDRS test, each participant underwent a laboratory examination to rule out any medical illness. Participants were evaluated every month along with clinical follow-up by their psychiatrists, who applied the HDRS test. Figure 1 represents a summary of the number of participants, the pharmacological treatment, and the changes to the protocol.

Drugs

Fluoxetine dose was 20 mg/d, which was established and adjusted by the psychiatrists. The medications used by patients were paid for by themselves.

Serum samples

Blood samples (10 mL) were collected by venipuncture from the cubital vein using Vacutainer® SST™ tubes with gel for serum separation (REF: 367988; BD Vacutainer System, Franklin Lakes, NJ, United States). Then samples were centrifuged immediately (1.125 × *g*) at 4°C for 15 min to obtain serum. Serum samples were aliquoted and stored at -80°C until use.

Chemokine measurements in serum

The serum levels of eotaxin, IL-8, IP-10, MCP-1, MIP-1α, and MIP-1β were measured in serum using the Bio-Plex Pro™ Human Cytokine 27-Plex Assay Kit per the manufacturer's instructions. Detection was performed using streptavidin-phycoerythrin and quantified on the Bio-Plex MAGPIX™ Multiplex Reader (Bio-Rad Laboratories Inc., Hercules, CA, United States). Chemokine concentrations were determined by interpolation using standard curves in Bio-Plex Manager™ (version 6.1; Bio-Rad Laboratories Inc.). The ranges of detection (pg/mL) reported by the manufacturer were as follows: Eotaxin: 2.1-24390, IL-8: 1.9-22233, IP-10: 3.0-34730, MCP-1: 2.0-23446, MIP-1α: 1.5-1773, and MIP-1β: 1.1-13533.

Statistical analysis

Statistical analysis was performed using GraphPad Prism, version 6.00 for MAC OS X (GraphPad Software, La Jolla, CA, United States). Homogeneity of variance and normality tests were applied initially, followed by one-way analysis of variance with the Bonferroni *post hoc* test. All values were expressed as mean ± standard deviation (SD). $P < 0.05$ was considered statistically significant.

RESULTS

Clinical parameters

Clinical and laboratory tests were performed in MDD adolescents and HVs in the clinical laboratory. The complete blood chemistry, blood count, complete urinalysis, and thyroid function test (T3, T4, and TSH) results were within normal reference value ranges. No differences between the groups were detected. Table 1 shows their demographics and recurrence rates, while psychiatric scale scores are presented in Table 2. At 0 wk, MDD patients had an HDRS score of 19.41 ± 4.72 points, compared with 9.13 ± 3.5 at 4 wk and 6.09 ± 2.4 at 8 wk.

Chemokines

The chemokine levels are shown in Table 2.

Table 1 Demographics and episodic data of the study sample

	HVs, *n* = 18	Patients, *n* = 22
Age in yr	18.9 ± 1.2	17.1 ± 2.3
Gender, male/female	4/14	4/18
BMI in kg/m^2	23.2 ± 2.1	23.1 ± 2.1
Education in yr	12.9 ± 1.2	11.5 ± 2.6
Family history, yes/no	3/15	8/14
First episode	N/A	8
Recurrent episode	N/A	14

Values are presented as mean ± standard deviation. BMI: Body mass index; HVs: Healthy volunteers; N/A: Not applicable.

Table 2 Clinical psychiatric scores and serum chemokine levels in adolescents with major depressive disorder in 8 wk of selective serotonin reuptake inhibitor treatment

Chemokine serum levels, pg/mL	HVs	Adolescents with MDD			*Post hoc* statistical analysis		
	n = 18	0 wk, *n* = 22	4 wk, *n* = 22	8 wk, *n* = 22	0 wk *vs* HVs	4 wk *vs* 0 wk	8 wk *vs* 0 wk
MCP-1 or CCL2	48.1 ± 3.7	107.7 ± 31.0	89.8 ± 19.9	102.9 ± 14.0	[d]*P* < 0.0001	[a]*P* < 0.05	NS
MIP-1α or CCL3	5.4 ± 1.0	7.3 ± 1.4	6.7 ± 1.4	7.4 ± 1.0	[d]*P* < 0.0001	NS	NS
MIP-1β or CCL4	204.7 ± 42.2	324.0 ± 61.5	311.8 ± 48.1	294.8 ± 34.8	[d]*P* < 0.0001	NS	NS
IL-8 or CXCL8	50.2 ± 6.8	79.2 ± 18.0	66.9 ± 13.2	73.3 ± 9.1	[d]*P* < 0.0001	NS	NS
IP-10 or CXCL10	1890.0 ± 52.7	2309.0 ± 545.1	2224.0 ± 578.5	2710.0 ± 220.1	[a]*P* < 0.05	NS	[a]*P* < 0.05
Eotaxin or CCL11	255.4 ± 50.4	319.8 ± 65.5	277.2 ± 51.8	328.6 ± 50.7	[b]*P* < 0.01	NS	NS
Clinical psychiatric scale							
HDRS	N/A	19.4 ± 4.7	9.1 ± 4.72	6.0 ± 2.4	N/A	[d]*P* < 0.0001	[d]*P* < 0.0001

Values are presented as mean ± standard deviation. To compare differences between means, the homogeneity of variance test was employed in all cases, followed by one-way analysis of variance with Bonferroni's *post hoc* test when the variances were equal and Dunnett T3 test when the variances were not equal. Statistical significance was attributed when
[a]*P* < 0.05;
[b]*P* < 0.01 and
[d]*P* < 0.0001. N/A: Not applicable; NS: Not significant. HDRS: Hamilton depression rating scale; IL-8: Interleukin-8; IP-10: Interferon gamma-induced protein 10; MCP-1: Monocyte chemoattractant protein-1; MDD: Major depressive disorder; MIP: Macrophage inflammatory protein.

MCP-1

MCP-1 is produced constitutively after induction by oxidative stress, cytokines, or growth factors and secreted by several types of cells, including monocytes, smooth muscle cells, and endothelial cells[20]. We observed significant differences in serum MCP-1 levels between HVs and patients (HV *vs* 0 wk, 4 wk, and 8 wk) (F = 34.03, *df* = 80.3, *P* < 0.0001). Before beginning pharmacological treatment (0 wk), patients showed significantly higher MCP-1 levels compared with HVs (*P* < 0.0001). Notably, MCP-1 declined in patients after 4 wk of fluoxetine administration (0 wk *vs* 4 wk, *P* < 0.026) but increased at 8 wk to similar levels as in 0 wk.

MIP-1α

Normally, MIP-1α is expressed by stromal and hematopoietic stem cells and participates in cell adhesion, migration, and chemotaxis of monocytes, lymphocytes, dendritic cells, eosinophils, and natural killer (NK) cells. It is also involved in the inflammatory process, inhibits stem cell proliferation, and is a potent osteoclast activator[21]. This protein recruits and stimulates mononuclear phagocytes in the CNS, microglia, and astrocytes, which are sources of this chemokine[22]. Serum MIP-1α levels were higher at all time points in patients compared with HVs (F = 10.01, *df* = 80.3, *P* < 0.0001), but not between the 8 wk clinical follow-up (4 and 8 wk) and the beginning of

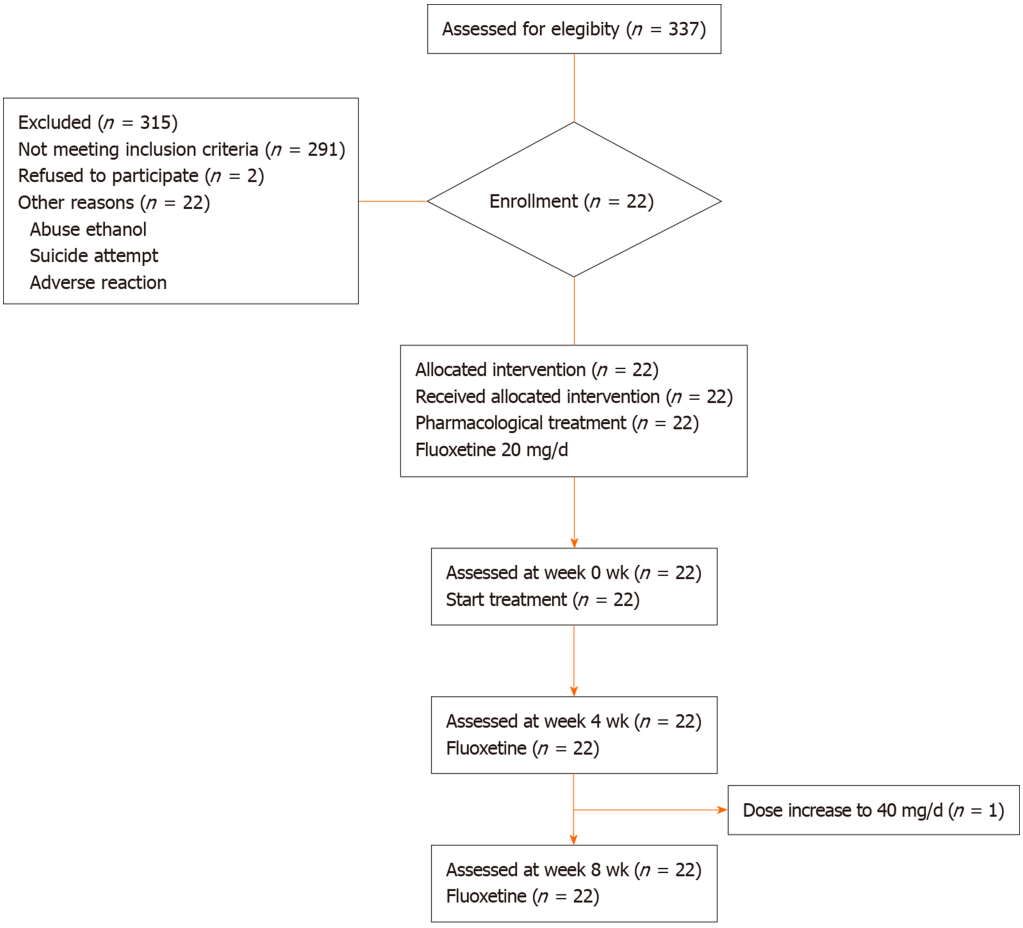


Figure 1 Flow diagram of 8-wk fluoxetine treatment for patients with major depressive disorder.

the pharmacological treatment (0 wk).

MIP-1β

MIP-1β has chemoattractive properties toward several cell types including immature dendritic cells, macrophages, monocytes, and NK cells. In addition, it induces calcium mobilization in NK cells, monocytes, leukocytes, vascular smooth muscle cells, and progenitor B cells[23]. We observed significantly higher levels of MIP-1β in patients *vs* HVs (F = 23.55, df = 80.3, $P < 0.0001$) but no differences throughout the clinical follow-up (0, 4, and 8 wk).

IL-8

IL-8 is a chemoattractant for neutrophils and lymphocytes in inflammatory processes. We noted significant differences in serum IL-8 levels between HVs and patients during the clinical follow-up (F = 12.74, df = 80.3; $P < 0.0001$). Patients experienced a significant decrease in IL-8 from 0 wk to 4 wk ($P < 0.01$), which increased at 8 wk to similar levels as those at 0 wk.

IP-10

IP-10 is a T helper cell 1-related chemokine identified as an early-response gene induced by interferon (IFN)-γ in U937 monocytes[24]. The IP-10 and IFN-γ levels detected in these same patients[25] showed a correlation ($r = 0.6147$, $P < 0.0001$), while IP-10 levels were higher in patients (0, 4, and 8 wk) *vs* HVs (F = 12.74, df = 80.3, $P < 0.0001$). However, IP-10 levels significantly increased in patients only at 8 *vs* 0 wk ($P < 0.01$).

Eotaxin

Eotaxin is the most potent and selective factor that modulates the function of eosinophils and mediates the infiltration of eosinophils into the airway[26]. Eotaxin is secreted primarily from bronchial epithelial cells, eosinophils, and endothelial cells. In our patients, serum eotaxin levels were higher than HVs at 0, 4, and 8 wk (F = 8.00, df

= 80.3, $P < 0.0001$). Serum eotaxin levels did not vary in patients throughout the clinical follow-up *vs* 0 wk.

DISCUSSION

Disturbances in serum chemokine levels are associated with the onset of major depression[9,12-14,27,28]. These inflammatory molecules affect cell-cell interactions, neuromodulation, and synaptic transmission, all of which are altered in MDD patients[13]. Although, a relationship between serum and cerebrospinal fluid levels of chemokines has not been demonstrated, the expression of some chemokines, chemokine ligands, and receptors in developing and mature CNS has been described under both physiological and inflammatory conditions. Astrocytes, oligodendrocytes, and microglia, as well as neuronal cells, constitutively release several chemokines including MCP-1, MIP-1α, MIP-3, secondary lymphoid-tissue chemokine, IP-10, and fractalkine[29,30].

Chemokines play an important role in the regulation of neuronal development and plasticity, proliferation, migration, and neural progenitor cell differentiation. For example, fractalkine regulates microglial synaptic pruning of mature neurons, modulates several neurotransmitters, and regulates the activation state of microglia[29,30]. Therefore, these molecules influence the development and plasticity of the CNS. Exogenous application of fractalkine enhances *in vivo* neurogenesis in aged rats by modulating the microglia phenotype. Other chemokines such as MCP-1, CCL21, and monokine induced by IFN-γ (MIG), promote neuronal differentiation, whereas MCP-1, growth-regulated oncogene-α, and MIG favor oligodendrocyte differentiation. Also, chemokines present a unique class of neurotransmitters and neuromodulators that regulate cell survival and synaptic transmission. Fractalkine, which co-localize with serotonin in neurons of the dorsal raphe nucleus, may indirectly inhibit serotonin neurotransmission by upregulating the sensitivity of serotonin dorsal raphe nucleus neurons to gamma-aminobutyric acid inputs. Furthermore, the results from electrophysiological studies suggest that MCP-1, regulated upon activation, normal T cell expressed and presumably secreted, macrophage-derived chemokine, MCP-5, IL-8, and fractalkine chemokines can modulate electrical activity in the cortical, cerebral, hippocampal, and hypothalamic neurons[29,30]. Given the number of functions in which chemokines and their receptors are involved in the CNS, they could become novel diagnostic markers or therapeutic targets for MDD, although a more significant number of studies is required.

In this work we measured serum levels of eotaxin, IL-8, IP-10, MCP-1, MIP-1α, and MIP-1β levels in adolescents with MDD throughout 8 wk of clinical follow-up. Although other groups have reported an association between peripheral chemokine levels and the severity of depressive symptoms, there are discrepancies in their results. Furthermore, our study is the first to report the chemokine profiles in adolescents with MDD.

MCP-1

Levels of MCP-1 were high in adolescents with MDD without treatment *vs* HVs, consistent with a meta-analysis[14]. Longitudinal studies, such as those by Sutcigil *et al*[31], have reported similar values for MCP-1 in HVs. Their results showed MCP-1 levels of 84.54 ± 12.54 pg/mL in HVs with a mean age of 34 treated with sertraline (another SSRI) for 8 wk, after which MCP-1 levels fell by over 50%[31]. In our clinical sample, posttreatment MCP-1 levels reached pretreatment values. Piletz *et al*[32] reported similar findings to ours, recording high levels of MCP-1 in MDD patients (205 ± 19 pg/mL) before treatment compared with HVs (132 ± 23 pg/mL). Their patients (mean age 39) were treated with venlafaxine, a dual antidepressant, for 8 wk after which MCP-1 levels remained constant[32].

Other groups, as Simon *et al*[17], reported high levels of MCP-1 in MDD patients before treatment. However, their results, in subjects with a mean age of 42, had a wide SD for HVs (56.66 ± 106.19 pg/mL) and MDD patients (191.00 ± 381.69 pg/mL)[17]. Moreover, four reports failed to detect changes in MCP-1 between patients and HVs[33-36]. All of these studies generated results from patients and controls aged over 40 and were included in the meta-analysis by Eyre *et al*[14]. Lehto *et al*[13] observed lower MCP-1 levels (27.19 pg/mL) in MDD patients *vs* HVs (40.79 pg/mL); these data were obtained in 61 MDD patients with a mean age of 54.

An *in vitro* study reported that the severity of depressive symptoms is significant and positively associated with the overexpression of MCP-1 and IL-8 in

lipopolysaccharide (LPS)-stimulated human blood monocytes[37], which partially explains the MCP-1 levels in our patients. Our data and those of Piletz *et al*[32] suggest that the administration of dual or selective antidepressants is insufficient to reduce MCP-1 levels in MDD patients after 8 wk, although Arreola *et al*[38] had contradictory findings. The significant decrease in MCP-1 in our patients after 4 wk with fluoxetine treatment suggests a partial effect of SSRIs on circulatory levels of this chemokine secreted by macrophages, which constitutively express serotonin transporter[38]. High levels of MCP-1 have been suggested to be early-stage indicators of endothelial damage and have been detected in coronary artery disease-associated chronic renal failure[32].

MIP-1α

Levels of MIP-1α were high in untreated adolescents with MDD compared with HVs and remained unaltered after 8 wk of fluoxetine treatment. No other longitudinal studies exist on this chemokine. Other groups have compared serum MIP-1α levels between adult patients and HVs, similar to Simon *et al*[17]. However, the values had a wide SD for HVs (60.33 ± 95.91 pg/mL) and MDD patients (463.8 ± 706.88 pg/mL) while Merendino *et al*[22] only detected MIP-1α in two of nine patients. Therefore, more studies on this chemokine in mood disorders are needed.

MIP-1β

Although MIP-1β has a similar response to MIP-1α, Lehto *et al*[13] reported significant lower levels of MIP-1β (45.41 ± 95.91 pg/mL) in 61 MDD patients with a mean age of 53 regarding HV levels (76.31 ± 9.84 pg/mL). Given the scarce information on this inflammatory protein, additional studies are necessary.

IL-8

IL-8 was elevated in adolescents with MDD without treatment compared with HVs, remaining at similar values despite fluoxetine treatment for 8 wk. A 2-year study including 1600 geriatric MDD patients in the Netherlands and Australia[16,39] reported that serum IL-8 levels correlate with depressive symptoms. No subsequent longitudinal studies have been performed. Other studies have reported high circulatory levels of IL-8 in patients with MDD[17,40].

In contrast, the meta-analysis by Eyre *et al*[14], which included seven studies from 1998 to 2012, assessed 560 MDD patients and concluded that there was no significant difference in serum levels of IL-8 between MDD patients and HVs ($P < 0.228$). An *in vitro* study by Suarez *et al*[37] reported that the severity of depressive symptoms was significant and positively associated with the overexpression of MCP-1 and IL-8 in LPS-stimulated human blood monocytes, which in part explains the IL-8 levels in our patients. IL-8 has been linked to low cognitive performance, suggesting that it has several effects on the CNS[39]. Notably, IL-8 crosses the blood-brain barrier in infectious processes[41].

IP-10

Our patients had significantly higher and constant levels of IP-10 than HVs during the first 4 wk of fluoxetine treatment; however, IP-10 rose significantly *vs* pretreatment levels by 8 wk and thus was the only molecule with this pattern. In contrast, Wong *et al*[42] reported differences in plasma levels of IP-10 in HVs (67.61 ± 1.16 pg/mL) and MDD patients (95.50 ± 1.16 pg/mL) before pharmacological treatment, whereas MDD patients experienced a decrease in IP-10 at 8 wk after beginning treatment with antidepressants (desipramine or fluoxetine). Further studies will be required to determine the behavior of this molecule in MDD patients.

In an *in vitro* study, Tsai *et al*[24] demonstrated that fluoxetine inhibits the secretion of IP-10 in TPH-1 cells (a cell line derived from human macrophages) that have been stimulated with LPS, in a process that is dependent on the mitogen-activated protein kinase-38 pathway. In contrast, after 8 wk on fluoxetine, IP-10 increased in our adolescents with MDD. These results are notable due to high levels of IP-10, an angiostatic factor with antifibrotic properties[9].

Eotaxin

In a comparison between patients and HVs, we observed a significant elevation in serum eotaxin levels, which remained high throughout the clinical follow-up. There are no other longitudinal reports on this chemokine; still, there are three transversal studies showing that MDD patients had significantly higher circulatory levels of eotaxin than HVs before pharmacological treatment[17,34,43].

It has been reported that plasma eotaxin levels are related with reduced neurogenesis in aged mice and that eotaxin levels rise in blood and cerebrospinal fluid of healthy aging humans[44]. Notably, in our study, eotaxin rose significantly in adolescents with MDD despite treatment with fluoxetine. As in other cases, there are few studies on eotaxin in mood disorders. Based on its effects in the CNS, eotaxin inhibits IL-4 activity[45] and IL-4 is critical in higher functions of the normal brain, such as memory and learning[46], cognitive functions that are affected in MDD.

In this study, we observed that chemokines eotaxin, IL-8, IP-10, MCP-1, MIP-1α and MIP-1β were increased in comparison with HVs, and despite treatment with fluoxetine, they remained consistently high in the patient group. Although there were variations in serum chemokine levels throughout the 8 wk clinical follow-up, all adolescents with MDD experienced a significant decrease in clinical-psychiatric parameters after consuming fluoxetine, similar to the two other longitudinal studies[31,32]. This knowledge confirms the approach that clinical-psychiatric scales only focus on the behavioral parameters and further work is necessary to identify molecular parameters of clinical utility for psychiatrists in mood disorders.

Limitation of this study

This study had some limitations. The patient number was small, although the numbers of HVs and patients were sufficient for statistical analysis. In all cases, the discrepancies between our values and those reported by other groups can be explained by differences in the sample source such as serum or plasma, detection techniques, age of the participants, and confounding factor, such as tobacco and alcohol consumption, and body mass index. Further studies will be required to validate our findings.

In conclusion, our results showed a significant elevation in serum chemokine level in adolescents with MDD despite treatment with fluoxetine and improvement in HDRS score. This prompted us to consider the multidisciplinary management of MDD patients since high levels of MCP-1 and IP-10 are associated with endothelial damage and coronary risk. The elevation in eotaxin, IP-10, and IL-8 might explain certain features of depressed patients such as impaired cognition, memory, and learning. Further studies are necessary to examine these findings and determine their implications for future therapeutic approaches in MDD patients.

ARTICLE HIGHLIGHTS

Research background

Major depressive disorder (MDD) affects 350 million people, approximately 6% of whom are adolescents; however, research on this age group is limited. The depressive symptomatology in adolescents can be confused with other psychiatric disorders, in turn affecting the proper diagnosis and normal development of patients. MDD in adolescents is associated with several negative outcomes including other psychiatric disorders later in life, educational impairment, self-injury, and suicide.

Research motivation

The immune system reaches maturity at about 16 years of age and upon the central nervous system second neural pruning. This makes adolescent patients with MDD have molecular characteristics that initially differ from adults and the elderly. These particularities have not been efficiently explored.

Research objectives

This study determined the differences in circulatory levels of eotaxin, interleukin (IL)-8, interferon gamma-induced protein (IP)-10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1α and MIP-1β in HVs and adolescents with MDD, and assessed the changes induced by antidepressants consumed during 8 wk of clinical follow-up, which is the minimum time to observe the therapeutic efficacy of selective serotonin reuptake inhibitors, like fluoxetine.

Research methods

We measured serum levels of eotaxin, IL-8, IP-10, MCP-1, MIP-1α, and MIP-1β in adolescents with MDD and performed a clinical psychiatric evaluation using the Hamilton depresión rating scale (HDRS). Eighteen HVs and twenty-two adolescents with MDD were monitored throughout 8 wk of clinical follow-up.

Research results

All evaluated chemokines decreased at 4 wk, but only MCP-1 and IL-8 differed significantly ($P < 0.05$) between 0 and 4 wk. In adolescents with MDD, all chemokines rose to their initial concentrations by 8 wk (*vs* 0 wk), but only IP-10 did so significantly ($P < 0.05$). All patients experienced a significant decrease in HDRS scores at 4 wk ($P < 0.0001$) and 8 wk ($P < 0.0001$) compared with 0 wk. Despite the consumption of fluoxetine, adolescents with MDD had significantly higher chemokines levels, even after considering the improvement in the HDRS score.

Research conclusions

Our results showed a significant elevation in serum chemokine levels in adolescents with MDD despite treatment with fluoxetine and an improvement in HDRS scores. This prompted us to consider the multidisciplinary management of MDD patients since high levels of MCP-1 and IP-10 are associated with coronary risk. The elevation detected in eotaxin, IP-10, and IL-8 serum levels might explain certain features of depressed patients such as impaired cognition, memory, and learning.

Research perspectives

Given the number of functions in which chemokines and their receptors are involved in the central nervous system, they could become novel diagnostic markers or therapeutic targets for MDD patients. However, a more significant number of studies are required, particularly in the adolescent population.

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SYSTEMATIC REVIEWS

Dietary modification in the treatment of schizophrenia spectrum disorders: A systematic review

Monique Aucoin, Laura LaChance, Sam N Clouthier, Kieran Cooley

ORCID number: Monique Aucoin 0000-0001-6804-5844; Laura LaChance 0000-0001-7630-8077; Sam N Clouthier 0000-0002-4656-5467; Kieran Cooley 0000-0001-7960-6504.

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Monique Aucoin, Sam N Clouthier, Kieran Cooley, Department of Research and Clinical Epidemiology, Canadian College of Naturopathic Medicine, Toronto M2K 1E2, Canada

Laura LaChance, Department of Psychiatry, McGill University, Montreal H3A 0G4, Canada

Laura LaChance, Centre for Addiction and Mental Health, Toronto M6R 1A1, Canada

Kieran Cooley, Department of Public Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo 2007, Australia

Kieran Cooley, Department of Doctoral Acupuncture and Chinese Medicine, Pacific College of Health Science, San Diego, CA 92108, United States

Corresponding author: Monique Aucoin, Research Fellow, Department of Research and Clinical Epidemiology, Canadian College of Naturopathic Medicine, 1255 Sheppard Ave E, Toronto M2K 1E2, Canada. maucoin@ccnm.edu

Abstract

BACKGROUND

Schizophrenia spectrum disorders impact functioning, reduce quality of life and increase the risk of physical illness and premature mortality. Nutritional intervention studies aimed at decreasing body weight have demonstrated efficacy in improving metabolic outcomes; however, few studies have explored the impact of interventions designed to modify diet on mental health outcomes.

AIM

To synthesize the existing experimental studies of adjunctive diet modification as an intervention in the treatment of psychotic disorders, analyze findings related to effectiveness and safety, highlight knowledge gaps and limitations, and set forward recommendations for future research studies.

METHODS

An extensive a priori search strategy was developed and the databases Embase, Embase Classic, Ovid MEDLINE were searched. Screening and data extraction were completed in duplicate. Studies included in this analysis were experimental studies of an adjunctive dietary intervention (overall dietary pattern or education on dietary change) for treatment of schizophrenia spectrum disorders. No restrictions were placed on control groups or blinding. The studies were required to report a mental health outcome.

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RESULTS

Twenty-five clinical trials were identified, along with two additional protocols and two meta-analyses. Nineteen of the clinical trials reported improvement in one or more mental health domain including psychosis symptoms, cognition, and quality of life. A high level of heterogeneity was found with respect to patient population, intervention, and study design. All of the studies included lifestyle or psychosocial components in addition to dietary modification. The nutrition advice provided to participants was poorly described overall and compliance was not assessed. The studies that showed benefit tended to have a smaller sample size and were less likely to be randomized but were more likely to use a group delivery intervention.

CONCLUSION

Further research assessing effectiveness and efficacy of clearly reported dietary interventions is warranted, especially those using rigorous methodology, modifying diet in isolation and assessing participant compliance.

Key words: Nutrition; Psychosis; Schizophrenia; Diet

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Core tip: While guidelines exist related to the role of nutrition interventions in the management of obesity and physical comorbidities in patient with schizophrenia spectrum disorders, there is limited clinical use in the management of mental health symptoms. This systematic review identified and analysed the findings of 25 clinical trials which modified participant diet and measured a mental health outcome. Nineteen reported improvement in one or more domain; however, many used additional interventions in combination with nutrition, and failed to report a detailed intervention protocol or assess compliance, limiting the conclusions that can be drawn. Further research is warranted using rigorous methodology.

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INTRODUCTION

Schizophrenia spectrum disorders (SSD) include schizophrenia, schizoaffective disorder, and other psychotic disorders. The etiology is largely unknown and likely multifactorial with genetic, biological, and social factors implicated. SSD symptoms include positive symptoms (including delusions and hallucinations), negative symptoms (including social withdrawal and apathy), depression, and cognitive symptoms. While many theories exist, these symptoms may be attributed to imbalances in neurotransmitters and their receptors, dysregulation of other neurochemicals such as brain derived neurotrophic factor (BDNF), immune dysregulation, neuro-inflammation, and mitochondrial and metabolic dysfunction[1-3]. Treatment of SSD includes a combination of pharmaceutical and psychosocial interventions including anti-psychotic medications.

Individuals with psychotic disorders are at significantly elevated risk of medical comorbidities, ultimately resulting in an estimated 8 to 20-year reduction in lifespan[4,5]. Several factors contribute to increased risk of mortality such as socioeconomic status, increased tobacco use, low quality diet, and metabolic complications caused by antipsychotic medication[6-10].

Guidelines and programs exist to support SSD patients in dietary choices to manage weight and physical illness; however, nutritional guidelines for the treatment of psychiatric symptoms do not exist. Nutritional psychiatry is a relatively recent field, studying the effects of nutrients on mental illness incidence and progression. An expanding body of evidence including observational[11], mechanistic, and intervention

studies[12,13] demonstrates a role of dietary constituents and patterns in the prevention and treatment of mental illnesses, although research in SSD is relatively limited.

Health care providers often accurately report obstacles faced by patients with SSD in the implementation of dietary interventions. Obstacles include motivational and cognitive barriers, poverty, as well as psychotic symptoms[14]. However, dietary intervention trials designed to improve aspects of physical health have documented feasibility and acceptability among SSD patients. One diet intervention study demonstrated an increased vegetable intake and decreased intake of discretionary foods and calories in first episode psychosis patients[5]. Another study involving participants with severe mental illness demonstrated improvements in diet quality and cardiovascular disease risk factors following a Mediterranean diet intervention[15].

Although fewer in number, some intervention studies have assessed mental health symptoms as primary or secondary outcomes. The purpose of the present systematic review is to synthesize the existing experimental studies of dietary modification as adjunctive treatment for psychotic disorders. We sought to analyze findings related to mental health outcomes (efficacy) and safety, highlight knowledge gaps and limitations, and set forward recommendations for future research studies.

MATERIALS AND METHODS

An extensive a priori search strategy was developed by an experienced medical information specialist through an iterative process, which included over 300 search terms. Supplementary material appendix 1 contains the full search strategy. The search was executed in Embase, Embase Classic, and Ovid MEDLINE on January 6, 2017 and updated on April 15, 2018 with the removal of a small fraction of search terms that had failed to yield useful results in the initial search (see appendix 1 for details). No limits were placed on language, publication status, or year of publication.

Eligible studies included experimental studies with an intervention that attempted to manipulate participants' overall dietary pattern (*e.g.*, "healthy diet", diet counselling, nutrition education), not just an individual type of food, dietary constituent or isolated component (*e.g.*, supplement studies, low carbohydrate diets, gluten-free diets). The studies included participants with psychotic disorders. No restrictions were placed on blinding or the presence of a control group. Studies were required to assess a mental health outcome; studies that measured only physical health outcomes were not eligible.

Title and abstract screening were completed, based on the above criteria, in duplicate using Abstrackr, an online open-source program that facilitates rapid screening decisions and concurrent tagging of results. Disagreement was resolved by consensus by the two principle investigators (Monique Aucoin and Laura LaChance). Studies that failed to meet inclusion criteria on full text review were excluded. Data was extracted in duplicate using a piloted template. The data extracted included: author name, year of publication, geographic location, presence of control group, use of randomization, use of blinding, study population, inclusion of individuals with additional psychiatric illnesses, sample size, intervention description, method of intervention delivery (group or individual), additional interventions provided simultaneously, mental health outcome reported, change in outcome, whether the mental health outcome was identified as the primary outcome, weight or other physical health outcome and adverse events. Because of the significant heterogeneity of the populations, interventions and outcomes, meta-analysis was not attempted. Studies were grouped based on whether or not a positive mental health outcome was reported, the primary outcome of interest. χ^2 test was used to assess for significance in the differences between these groups of studies based on study design and factors which may contribute to bias.

The search strategy was initially designed for the conduct of a larger scoping review on the topic of dietary factors and psychosis which has been previously published[16].

On January 20, 2020, a search update was completed for any additional studies that met criteria for the present systematic review. Because this update was completed exclusively for the present review, a modified search string using the following terms was executed: (Diet or Dietary or Nutrition or food) and (psychosis or psychotic or schizophrenia).

RESULTS

The initial search and updates identified 76889 results, which were reduced to 55330 after de-duplication. Using Abstrackr to facilitate screening allowed study authors to manually screen slightly less than 50% of results (26053), relying on the artificial intelligence feature of the program to screen the remaining articles. 1290 articles were assessed in full-text form with 822 meeting criteria for the scoping review. Of these, 27 manipulated the dietary pattern of participants and met criteria for inclusion in the present systematic review. The update of the search January 2020 yielded 356 results, of which two met criteria for inclusion (Figure 1).

Description of studies

The majority of the studies were published between 2015 and 2019 (Figure 2).

Overall, most of the studies were published in the United Kingdom and Europe followed by North America with the remaining published in Australia, Asia, and South America.

Methodology

Three publications described study protocols. The results of one of these protocols were described in another publication. Two studies were meta-analyses. The remaining twenty-five studies were completed clinical trials. Of those, four studies employed both blinding and randomization. An additional five studies used a control group and randomization but no blinding. Another six studies used a control group but lacked randomization and blinding. The remaining ten trials were completed with no control group (Table 1)[17-41].

Sample size

The average sample size of the completed studies was 171.8; however, there was significant heterogeneity (SD = 191.5, range: 8 to 770).

Duration

The mean duration was 33.4 wk (SD = 31). Most studies used an intervention which lasted between four months and one year. Two studies lasted two years or longer.

Interventions

The details of the interventions themselves were generally poorly described. Most of the interventions consisted of nutritional education that focused on healthy diet habits. Some programs reported more specific macronutrient recommendations while other emphasized general concepts like meal planning and goal setting. Three interventions involved following specific energy-restricted diets. An additional three interventions mentioned education about calories. The interventions were mainly group-based. Five trials implemented interventions that had both individual and group components and five trials consisted of individual interventions only. It was unclear if the interventions were individual or group-based in two of the studies. Nearly all studies failed to identify the qualifications or training of the individual(s) delivering the interventions.

In most of the studies, the participants continued to take their psychiatric medications. All studies supplemented the dietary interventions with exercise and/or psychosocial interventions such as motivational interviewing, smoking cessation, or peer support. The additional interventions that were used alongside diet are displayed in Figure 3.

Population

Seventeen of the twenty-five studies recruited patients with a diagnosis of schizophrenia, SSD, or psychosis. Two of the studies included participants who were taking an antipsychotic medication, regardless of their specific psychiatric diagnosis. Ten of the studies included participants diagnosed with schizophrenia in combination with other mental illnesses such as bipolar disorder, anxiety disorder, major depressive disorder, or personality disorders. Of those, one study required a co-morbid substance-use disorder diagnosis. One study was completed on healthy children who were followed to monitor the development of schizotypal personality traits or antisocial behaviour at ages 17 and 23.

Most of the interventions were carried out in an adult population. One study recruited teenagers (ages 13-17), one recruited youth experiencing early psychosis and one study included children (ages 3-5).

Eight of the studies required participants to have a weight concern such as recent

Table 1 All included studies

Ref.	Control	Random-ization and Blinding	Population	Sample size	Intervention	Mental health primary outcome	Duration (wk)	Symptom	Direction of Findings
Studies with one or more positive outcomes									
Usher *et al*[17], 2019	TAU	None	Youth, early psychosis	33	Behaviour intervention teaching mindfulness meditation, cooking classes, supermarket trips, fast-food learning, nutrition education, exercise, moderated group discussion to facilitate healthier living	Yes	12	Positive symptoms (Quick Scale for the Assessment of Negative Symptoms)	Improvement
Osborn *et al*[18], 2018	TAU	Randomized, single blind	Bipolar disorder (50%), schizophrenia (30%) or psychosis (20%); elevated cholesterol and 1 + modifiable risk factors for CVD	327	Manualized intervention to decrease cholesterol and CVD risk: Adherence to statins, improve diet and activity, reduce alcohol, quit smoking	No	52	Psychiatric In-patient costs	Improvement
								QOL (Warwick-Edinburgh Mental Well-being Scale)	Null
Hjorth *et al*[19], 2017	None	None	Chronic schizophrenia	45	Lifestyle program including nutrition, meal planning, walking/running group, smoking cessation, MI. individual and group components	No	120	QOL (WHOQoL)	Null
			Newly diagnosed schizophrenia	123				QOL (WHOQoL)	Improvement
Juel *et al*[20], 2017	None	None	Psychotic disorder, affective disorder, anxiety disorder, or developmental disorder with comorbid substance use or dependence; 12.5% SSD	64	Nutrition, exercise and smoking cessation program. Includes health diet habits, reading nutrition labels, macronutrient recommendations. Includes individual and group components	No	24	QOL (WHOQoL)	Improvement
								Medication Usage	Worsening
Masa-Font *et al*[21], 2015	TAU	None	Schizophrenic, schizoaffective or bipolar, treated with antipsychotic drug (67% SSD); BMI > 25	332	Group nutrition education and exercise sessions	No	12	QOL (SF-36)	Improvement
Farhat *et al*[22], 2016	None	None	Schizophrenia	8	Group educational program including nutritional balance, meal planning, budgeting, meal preparation, socialization	Yes	16	Negative (PANSS)	Improvement
								Cognitive (BECS)	Null
Provencher *et al*[23], 2016	Waitlist	None	SMI including psychotic disorders; weight concern	47	Program teaching nutrition and cooking	No	12	QOL	Improvement
Sauvanaud *et al*[24], 2016	None	None	Schizophrenia	14	Group educational program/ psychosocial program including schizophrenic disease, treatments, relationships to family, diet, social issues, relaxation	Yes	15	Functioning (GAF)	Improvement
								QOL (SQoL)	Improvement
								Medication Adherence (MARS)	Improvement

								Insight (French IQ8)	Null
Stiekema *et al*[25], 2014	TAU	Treatment centers randomized	Patients with severe mental illness (primarily SSD), inpatient	130	Group diet and exercise intervention: Lifestyle intervention to change the obesogenic environment within residential setting (*e.g.*, Whole grain bread available)	No	12	Depression	Improvement
								Psychological functioning	Improvement
								QOL	Worsening
Robertson *et al*[26], 2014	None	None	Schizophrenia-spectrum	25	Group healthy lifestyle group, walking group, grocery shopping	Yes	12	Psychotic symptoms (PANSS)	Improvement
Bralet *et al*[27], 2013	None	None	Schizophrenia	10	Group nutrition education, cognitive remediation, social skills, meal preparation	Yes	17	Psychotic symptoms (PANSS)	Improvement
								Self Esteem	Improvement
								Cognition (BACS, STICCS)	Improvement
Kuo *et al*[28], 2012	TAU	None	Schizophrenia	63	Group weight reduction program including food recommendations (more vegetables and monounsat fats, less sugar and calories), exercise, behaviour therapy	Yes	10	Biologic (BDNF)	Improvement
								Psychotic symptoms (BPRS)	Null
Porsdal *et al*[29], 2010	TAU	None	Schizophrenia or bipolar I, taking psychotropic medication	373	Group nutrition and exercise program	Yes	12	QOL (15D)	Null
								Psychotic symptoms (CGI-S)	Improvement
Van Citters *et al*[30], 2010	None	None	DMS-IV Axis I or II diagnosis; 18% SSD	76	Individualized health promotion program: health eating, exercise social inclusion, decrease calories. Includes individual and group components	No	36	Mental health functioning (SF-12)	Improvement
								Negative symptoms (SANS)	Improvement
Gretchen-Doorly *et al*[31], 2009	None	None	Schizophrenia	9	Nutrition (avoid high fat food, increase fiber, strategies for weight loss), exercise and stress management coaching	Yes	6	Self-efficacy for health practices, psychological wellbeing, health responsibility	Improvement
Castiglioni *et al*[32], 2008	Monthly clinical exam	None	Psychotic disorders	26	Group health and Wellness program	No	24	QOL (Quality of Life Index)	Improvement
Guimarães *et al*[33], 2008	TAU	None	Schizophrenia	67	Calorie-restricted diet; reduction in saturated fat and sugar, increase in fruit and vegetables. Individual delivery	No	4	BDNF	Improvement
Raine *et al*[34], 2003	TAU	Randomized	Children aged 3-5 years, no diagnosis	438	Group nutrition, education and physical exercise program: structured nutrition program provided the children with milk, fruit juice, a hot meal of fish or chicken or mutton, and a salad each day	Yes	104	positive schizotypal personality (Schizotypal personality questionnaire)	Improvement
								Cognition (Schizotypal personality	Improvement

								questionnaire)	
Aquila *et al*[35], 2000	None	None	Inpatients with severe persistent mental illness taking atypical antipsychotics	32	Group diet intervention to decrease fat, calories, sugar, snacking	No	78	Negative (subjective assessment)	Improvement
Studies without positive outcomes									
Holt *et al*[36], 2019	TAU	Randomization	Schizophrenia, schizoaffective disorder or first-episode psychosis, antipsychotic medication, BMI > 25 or concern about weight	412	Education on nutrition, physical activity and weight management. individual and group components	No	40	Depression Psychotic symptoms (BPRS)	Null Null
Stiekema *et al*[37], 2018	TAU	Randomized, Blinded	Psychotic disorder, mood disorder, personality disorder, anxiety, substance use disorder, developmental disorder or psychiatric comorbidity; 74% SSD; inpatient	770	Diet and exercise lifestyle intervention to adjust obesogenic environment (offer low-fat cheese, whole wheat alternatives, less sweets, smaller portions of snacks, fresh rather than canned vegetables) Includes individual and group components	Yes	52	Psychotic symptoms (PANSS) QOL (MANSA) Depression (CDSS)	Null Worsening Null
Naslund*et al*[38], 2017	Gym membership	Randomized	Major depressive disorder, schizoaffective disorder, or schizophrenia; 46% SSD	343	Individual nutrition, MI, fitness goal setting	Yes	52	Depressive Symptoms (CESD)	Null
Detke *et al*[39], 2016	Single 15-min session of basic information	None	Schizophrenia or Bipolar I	203	Individual intense behavioural weight counseling – nutrition education, pedometer, motivational enhancement, guidance on caloric restriction, low-fat, nutrient dense foods in moderate portion sizes	No	52	Psychotic symptoms (BPRS-C)	Null
Speyer *et al*[40], 2016	TAU	Randomized, blinded	Schizophrenia, schizoaffective disorder or persistent delusional disorder, abdominal obesity	428	Individual lifestyle program teaching healthy diet, cooking, smoking cessation, physical activity, coordination of care for somatic health	No	52	Psychotic symptoms (SANS and SAPS) Perceived health and stress Cognition (BACS) QOL (MANSA/Euro QoL)	Null Null Null Null
Jones *et al*[41], 2007	None	None	Taking antipsychotic medication	50	Group psychoeducation and physical activity program including nutrition, budgeting, cooking, goal setting	No	10	QOL (SF-36)	Null

BACS: Brief Assessment of Cognition in Schizophrenia; BDNF: Brain-derived neurotrophic factor; BMI: Body mass index; BPRS: Brief psychiatric rating scale; CDSS: The Calgary Depression Scale for Schizophrenia; CESD: Center for Epidemiological Studies Depression scale; CVD: Cardiovascular disease; GAF: Global Assessment of Functioning; MANSA: Manchester Short Assessment of Quality of Life; MARS: Medication Adherence Rating Scale; MI: Motivational interviewing; PANSS: The Positive and Negative Syndrome Scale; QOL: Quality of life; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SF-12: 12-Item Short Form Health Survey; SF-36: The 36-Item Short Form Health Survey questionnaire; SMI: Severe mental illness; SSD: Schizophrenia spectrum disorders; STICCS: Subjective Scale to Investigate Cognition in Schizophrenia; TAU: Treatment as usual; WHOQoL: World Health Organization Quality of Life –Brief.

weight gain or a body mass index (BMI) or waist circumference above a certain level.

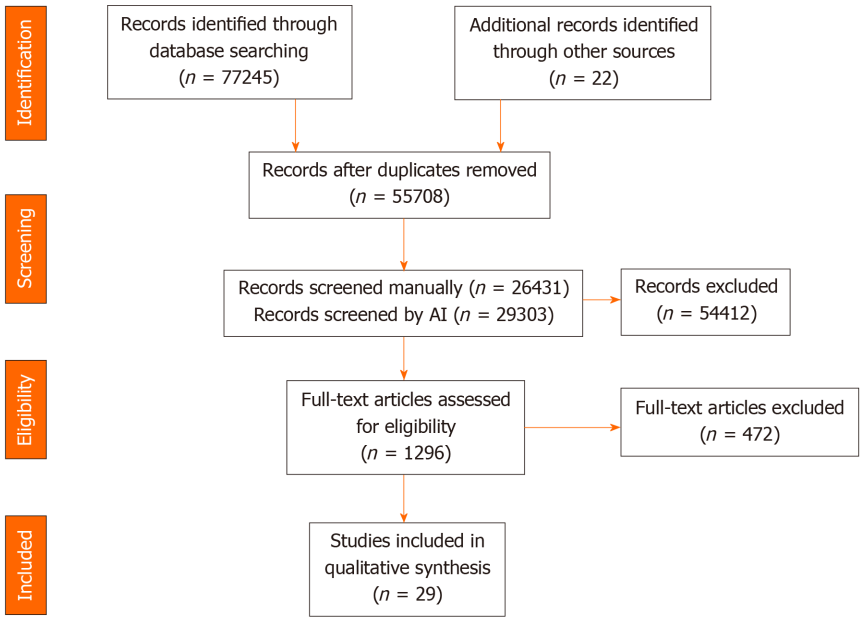


Figure 1 PRISMA flow chart.

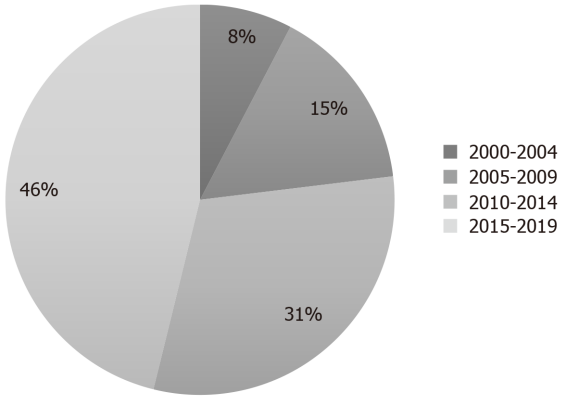


Figure 2 Distribution of studies based on year of publication.

Three studies involved participants in a supportive housing or clinical care facility, the remaining studies were completed with community-dwelling participants.

Outcomes

Of the 27 study protocols described, twelve were designed with mental health symptoms as the primary outcome. The remaining studies described the mental health outcomes as secondary or exploratory.

Outcome measures included quality of life, psychosis symptoms, cognitive symptoms, self-esteem, functioning, depression, mental healthcare service utilization and levels of the biomarker BDNF. Nineteen studies reported at least one positive mental health outcome (Figure 4, Table 1). While several studies reported changes in total psychosis symptoms, three reported improvements in negative symptoms and one in positive symptoms. The prospective intervention trial that assessed prevention of psychotic symptoms in children reported a decrease in positive symptoms at the later outcome assessment[34]; however, given that this study's design was significantly different compared to the others in this review, these results may be considered separately from the other studies reviewed.

Studies that did not report a positive mental health outcome were more likely to include 200 or more participants, use a control group or randomization, or include participants with diagnoses other than schizophrenia. They were more likely to

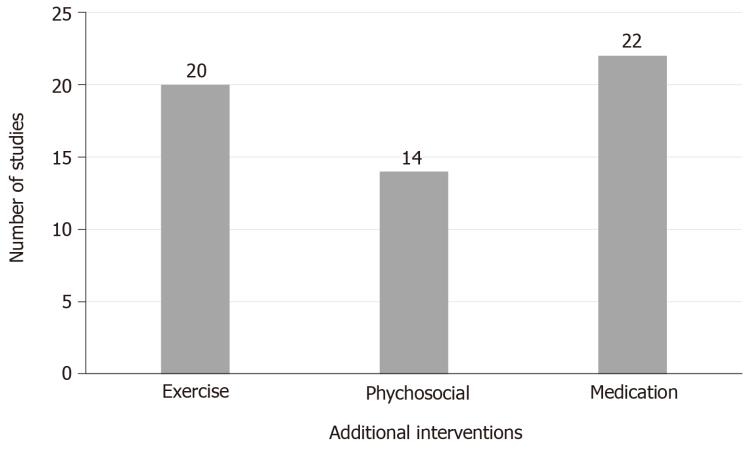


Figure 3 Additional interventions used alongside dietary modification in 25 studies.

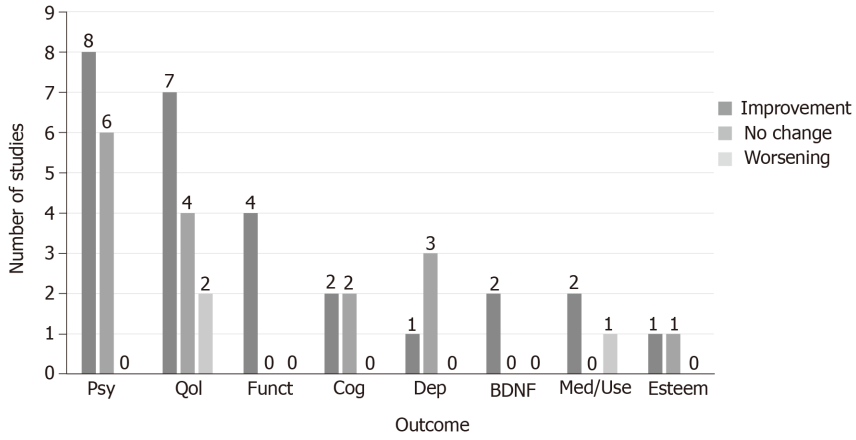


Figure 4 Direction of findings for specific outcomes. Psy: Psychotic symptoms; QoL: Quality of life; Funct: Functioning; Dep: Depression; Med/use: Medication use or mental health care utilization; Esteem: Self-esteem/self-efficacy/perceived health.

involve one-on-one intervention rather than group intervention. Compared with those showing benefit, they were less likely to cite mental health symptoms as a primary outcome and less likely to report positive findings in an outcome related to body weight. The differences between studies reporting a benefit to mental health outcomes and those that did not are reported in Table 2. The differences in sample size, group *vs* individual intervention format and, randomization achieved statistical significance.

With respect to duration of the effect, one study reported that positive mental health and weight outcomes persisted at a six month follow up assessment[32], the remainder did not report on long term outcomes.

A meta-analysis of six lifestyle intervention studies, including 289 participants, evaluated changes in levels of peripheral serum and plasma BDNF in patients with SSD and reported some positive findings compared to a control group[42]. A meta-analysis of 25 lifestyle intervention studies, including 1518 SSD participants, reported improvement in depression symptoms[43].

In addition to assessing mental health outcomes, 18 studies assessed physical health outcomes such as body weight, blood pressure, serum cholesterol, waist circumference, oral glucose tolerance, serum cytokine levels, and glycosylated haemoglobin. Nine of 18 studies found improvements in at least one physical measure with body weight, BMI and waist circumference most likely to benefit. It should be noted, that this represents a subset of the research on this topic; studies assessing exclusively physical outcomes were excluded from this review.

Adverse events

Adverse events were not generally reported. One study commented on adverse events

Table 2 Characteristics of studies that reported benefit in mental health outcomes and those that did not

	Number of studies reporting benefit (%)	Number of studies not reporting benefit (%)	*P* value
Studies with greater than 200 participants	4 of 19 (21)	5 of 6 (83)	0.00559
Studies that included patients with non-SSD diagnoses (*e.g.*, Depression, Bipolar, substance use disorder)	8 of 19 (42)	4 of 6 (67)	0.29380
Studies with an individual intervention component	2 of 19 (11)	3 of 6 (50)	0.03509
Studies designed with primary outcome related to mental health	9 of 19 (47)	2 of 6 (33)	0.54599
Studies that used a control	10 of 19 (53)	5 of 6 (83)	0.18081
Studies that used randomization	3 of 19 (16)	4 of 6 (67)	0.01553
Studies with positive finding in an outcome related to body weight	7 of 10 (70)	1 of 4 (25)	0.12428

that were medication-induced and not attributed to the intervention[39]. Another trial noted an increase in psychotropic medication use over the course of the assessment period[20]. An additional trial commented on deterioration of mental well-being in the intervention group[37]. Finally, one of the studies found that there were three deaths in the intervention group and they were not considered a result of the intervention; any other adverse events were similar between the treatment and the control groups[36].

DISCUSSION

This systematic review identified the clinical trials which have attempted to modify dietary patterns in patients with SSD and reported mental health outcomes in response to treatment. The results suggest that these interventions may have promise for improving mental health symptoms in SSD patients. However, there are significant limitations to these studies and opportunities for further research.

Twenty-one of 27 primary and secondary research studies reported significant improvement in terms of quality of life, symptom improvement, increased functioning, decrease mental healthcare utilization and/or improved cognition. Studies with positive findings were generally less likely to include other patient populations (non-SSD), were more likely to have a group component; however, they tended to include smaller sample sizes and were less likely to be randomized.

Adverse events were often not reported and if they were reported, they were not attributed to the dietary intervention itself. Two studies reported worsening mental health in response to treatment. One study[20] noted that participants had to increase their use of medication during the trial. The medication that was typically increased was quetiapine (Seroquel), which is also used as a sleep aid. The authors theorized that the increase in medication may be due to sleep issues rather than increasing psychiatric symptoms as the participants' sleep did worsen in the trial, possibly attributed to the various stages of withdrawal from substance use. The other study[37] noted that Quality of Life decreased in the intervention group. They attributed this to significant differences in levels of depression at baseline (non-optimal randomization) and a possible regression towards the mean. Furthermore, although the decrease in quality of life was statistically significant, it may not have been clinically relevant as it was a decrease of 1.5 points, on a scale with a range of 12-84 points.

Many of the studies utilized a group setting for the intervention. There is significant research suggesting a role of peer support and motivation in behavioural change[44,45]. In this review, studies using group interventions were more likely to report positive findings. Group delivery of interventions has the added benefit of cost effectiveness[46].

A significant limitation of this body of research is the generally small sample size and low methodological quality; few studies used randomization, blinding, or control groups. However, the most significant limitation is that all studies used multi-modal interventions rather than diet alone. These included exercise, psychosocial interventions, and smoking cessation in addition to medication. As the first two have significant evidence for a role in promoting improved mental health in SSD, it creates difficulty in understanding the exact role that diet modification may have played in achieving the outcomes reported.

Additionally, many of the studies were designed to test interventions for weight

loss or other physical conditions such as hypertension, dyslipidemia and glucose dysregulation. Mental health outcomes were secondary or exploratory in most of the studies. As a result, studies may have been statistically powered to detect changes in the primary physical outcomes and not the mental health outcomes.

A significant limitation of this body of evidence is in the reporting of the diet interventions tested. Nineteen studies described the intervention as "a healthy diet" or "nutrition education". While some studies provided details about the goals of the intervention (such as increased vegetable intake, decreased saturated fat intake), the majority of studies did not. Scientific understanding of a "healthy diet" has changed over time. For example, the American Dietary Guidelines removed cholesterol as a nutrient of concern in 2015 due to lack of evidence that dietary cholesterol impacts serum cholesterol levels[47]. However, previous guidelines had advised patients on limiting exposure to this nutrient. While certain dietary factors such as vegetables and fiber have been consistently viewed as healthy, fats and carbohydrates have experienced shifting attitudes over the previous decades[48]. As a result, studies designed at different times may have recommended significantly different macronutrient ratios. In addition to the role of macro- and micro-nutrients, a body of evidence has identified inflammation, oxidative stress, glycemic balance, food sensitivities, and the gut microbiome as intermediate factors between diet and mental health[49]. These various factors make it difficult to interpret the studies included in this review. It is possible that unique interventions with differing impacts on these pathophysiologic mechanisms contributed to the differing outcomes between studies. Future research may benefit from application of reporting checklists designed to improve the reporting of interventions[50]. A recent systematic review of methodology reporting in lifestyle interventions among people with psychosis also found generally incomplete reporting and put forward a recommendation for use of the CONSORT statement in future publications[51].

While it has been demonstrated that diet patterns in this patient population can be changed in response to nutrition education and counseling, it is widely acknowledged that this is challenging[14]. The lack of compliance data in the studies using educational programs and diet counselling creates significant difficulty in interpreting this body of evidence. It is possible that variability of compliance with the dietary interventions across studies could in part explain differing outcomes reported. Four studies included the provision of some or all of the participants' food intake and thus had a higher degree of control. These included the prospective prevention study in children and three studies which took place in in-patient settings. Although these studies involved modification to the available food options, there was still a degree of control exercised by participants with respect to the food they consumed. Of note, three of these four studies reported benefit.

Further research should include assessment of compliance. In designing further studies, researchers could consider subjective assessment tools such as the Mediterranean Diet score or Alternative Healthy Eating Index[52] or objective assessment approaches such as plasma vitamin C and serum carotenoids[53] or metabolomic analysis[54]. While speculative, the non-significant association found between studies showing benefit in both mental health and physical health outcomes could be related to participant compliance. Alternatively, the improvement in mental health symptoms may be related to changes in weight, as a bidirectional relationship between the two is known[55]. In the absence of information related to intervention uptake, the studies showing a lack of change to mental health outcomes cannot conclude that diet does not impact psychosis and other mental health outcomes but rather that the educational intervention provided was not able to elicit these changes.

The results of this body of evidence suggest that diet may be a modifiable target for the treatment of psychotic disorders alongside treatment as usual. Dietary interventions were associated with improvements in psychosis symptoms, quality of life, and functioning in some studies. Improved nutrition has also been shown to improve the physical health in a population at high risk of medical illness[5]. There are studies reporting no effect of dietary intervention. These inconsistencies may be attributable to heterogeneity in dietary interventions (including the multi-modal nature), unclear participant compliance with educational interventions and heterogeneous participant populations.

Nutritional interventions have a few clear benefits. They are relatively low in cost, low in risk, and have the potential to benefit the highly prevalent and costly physical comorbidities of schizophrenia spectrum disorders. When interpreted in combination with the more advanced research in other psychiatric populations, such as randomized controlled trial of adjunctive dietary interventions in major depressive disorder, there is justification for more research in this area.

Future studies should aim to examine adjunctive dietary modification without manipulation of other health behaviours, assess compliance using subjective or objective methods, include more homogeneous patient populations, identify mental health symptoms as primary outcomes and be powered accordingly. In addition, high quality experimental studies with a control group, blinding, and randomization are needed in this area of research alongside continuing research exploring effectiveness in real world scenarios. Lastly, in reporting on these studies, clearer description of the experimental dietary interventions would assist in interpreting results, duplication of findings, and guiding further research.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia spectrum disorders (SSD) impact functioning, reduce quality of life and increase the risk of physical illness and premature mortality. Several observational and preclinical studies suggest a role of diet in the development and progression of SSD and rigorous clinical trials designed to assess the impact of adjunctive diet interventions in patients with major depression have reported benefit.

Research motivation

Nutritional intervention studies aimed at decreasing body weight have demonstrated efficacy in improving metabolic outcomes; however, few studies have explored the impact of interventions designed to modify diet on mental health outcomes. Systematic review of this body of literature has not been previously conducted.

Research objective

This systematic review sought to synthesize the existing experimental studies of adjunctive diet modification as an intervention in the treatment of psychotic disorders, analyze findings related to effectiveness and safety, highlight knowledge gaps and limitations, and set forward recommendations for future research studies.

Research methods

An extensive a priori search strategy was developed and the databases Embase, Embase Classic, Ovid MEDLINE were searched. Screening and data extraction were completed in duplicate. Studies included in this analysis were experimental studies of an adjunctive dietary intervention (overall dietary pattern or education on dietary change) for treatment of SSD. No restrictions were placed on control groups or blinding. The studies were required to report a mental health outcome.

Research results

Twenty-five clinical trials were identified, along with two additional protocols and two meta-analyses. Of the 25 clinical trials, four employed both blinding and randomization. Five studies used a control group and randomization but no blinding while another six studies used a control group but lacked randomization and blinding. The remaining ten trials were completed with no control group. The average sample size was 171 participants and the average duration was 33 wk. The interventions consisted primarily of nutritional education; however, the nutrition advice provided to participants was poorly described overall and compliance was not assessed. All of the studies included lifestyle or psychosocial components in addition to dietary modification. Of the 27 protocols, twelve were designed with mental health symptoms as the primary outcome. A high level of heterogeneity was found with respect to patient population, intervention, and study design. Nineteen of the clinical trials reported improvement in one or more mental health domain including psychosis symptoms, cognition, and quality of life. The studies that showed benefit tended to have a smaller sample size and were less likely to be randomized but were more likely to use a group delivery intervention. Adverse events were not generally reported.

Research conclusions

The findings of this systematic review suggest that adjunctive diet interventions may be useful in the management of mental health symptoms in SSD; however, limitations in the existing research preclude clear conclusions.

Research perspectives

Further research assessing effectiveness and efficacy of clearly reported dietary interventions is warranted, especially those identifying mental health symptoms as their primary outcome, using rigorous methodology (control group and blinding), modifying diet in isolation from other health behaviours and assessing participant compliance.

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ABOUT COVER

Editorial board member of *World Journal of Psychiatry*, Dr. Wei Wang is a Full Professor of Personality Psychology at the Norwegian University of Science and Technology. Dr. Wang undertook his postgraduate training at Université de Liège (Belgium), receiving his DSc in 1995. Later, Dr. Wang successively joined the First University Hospital of University of Science and Technology in Hefei, China, the Zhejiang University School of Medicine in Hangzhou, China, and the Norwegian University of Science and Technology in Trondheim, Norway. Dr. Wang and his crew members focus their career efforts on personality traits and disorders, emotion components and disorders, dream experiences (nightmare and sexual dream) and disorders, and neurocognitive processes at cerebral and brainstem levels. His clinical research involves the personality disorders, bipolar I and II disorders, schizophrenia, and the like. (L-Editor: Filipodia)

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ORIGINAL ARTICLE

Observational Study

Alcohol and drug use disorders in adult attention-deficit/hyperactivity disorder: Prevalence and associations with attention-deficit/hyperactivity disorder symptom severity and emotional dysregulation

Espen Anker, Jan Haavik, Trond Heir

ORCID number: Espen Anker 0000-0003-4960-1715; Jan Haavik 0000-0001-7865-2808; Trond Heir 0000-0001-9616-0145.

Author contributions: Anker E and Heir T designed the study; Anker E collected and analyzed the data; Anker E, Haavik J, and Heir T actively participated in the writing of the manuscript; all authors approved the final draft.

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Espen Anker, Oslo ADHD clinic, Oslo 0366, Norway

Jan Haavik, Department of Biomedicine, University of Bergen, Bergen 5007, Norway

Jan Haavik, Division of Psychiatry, Haukeland University Hospital, Bergen 5021, Norway

Trond Heir, Institute of Clinical Medicine, University of Oslo, Oslo 0316, Norway

Corresponding author: Espen Anker, MD, Oslo ADHD Clinic, Kirkeveien 64B, Oslo 0366, Norway. espen.anker@online.no

Abstract

BACKGROUND

High risk of alcohol and drug use disorders in people with attention-deficit/hyperactivity disorder (ADHD) calls for exploratory research of relationships with clinical features of ADHD.

AIM

To estimate prevalence of alcohol/drug use disorders and associations with ADHD symptom severity and emotional dysregulation, in adults with ADHD.

METHODS

This observational cross-sectional clinical study consisted of patients admitted to a private psychiatric outpatient clinic in Oslo, Norway (2014-2018). Five-hundred and fifty-eight eligible patients diagnosed with ADHD (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria) agreed to participate. Alcohol and drug use disorders were diagnosed using the Mini International Neuropsychiatric Interview (MINI). Dependence and abuse were merged into "use" disorder as in MINI version 7.0/DSM-5. Questions were related both to lifetime and the past 12-mo. ADHD severity was assessed by the Adult ADHD Self Report Scale (ASRS). Subdivisions of the ASRS questionnaire as inattentive items and hyperactive/impulsivity items were recorded separately. Emotional dysregulation was assessed by the eight-item version of Barkley's Current Behavior Scale - Self Report.

Medice and Biocodex; Trond Heir reports having no competing interests.

Data sharing statement: Data are from a private psychiatric outward in Oslo. Public availability would compromise privacy of the respondents. According to the approval from the Norwegian Regional committees for medical and health research ethics, the data is to be stored properly and in line with the Norwegian Law of privacy protection. However, anonymized data is freely available to interested researchers upon request, pending ethical approval from the ethics committee. Interested researchers can contact project leader Espen Anker (espen.anker@online.no) with requests for the data.

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RESULTS

The 12-mo prevalence was 5.3% for alcohol use disorder and 13.7% for drug use disorder. The lifetime prevalence was 12.0% for alcohol use disorder and 27.7% for drug use disorder. Men had higher rates of both alcohol use disorder and drug use disorder compared to women. The prevalence of drug use disorder was more than twice that of alcohol use disorder for both sexes. The drugs most participants reported having used were (in descending order): Amphetamine (19.1%), cannabis (17.1%), cocaine or ecstasy (7.4%), benzodiazepines (7.4%), and heroin or other opioids (2.9%). Lifetime drug use disorder was significantly associated with both hyperactivity-impulsivity symptoms and emotional dysregulation symptom severity. Lifetime alcohol use disorder, on the other hand, was not significantly associated with ADHD symptoms or emotional dysregulation when adjusted for gender and age.

CONCLUSION

Patients with ADHD have a high lifetime prevalence of drug use disorder, which is associated with higher levels of hyperactivity-impulsivity symptoms and emotional dysregulation.

Key Words: Attention-deficit/hyperactivity disorder; Adult ADHD Self Report Scale; Emotional dysregulation; Substance use disorder; Alcohol use disorder; Drug use disorder

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Core Tip: High rates of alcohol and drug use disorders in people with attention-deficit/hyperactivity disorder (ADHD) needs further explanation. In this study of adult ADHD patients in clinical practice, we found a remarkably high incidence of past or current drug use disorder, especially for amphetamine and cannabis. Drug use disorder but not alcohol was associated with clinical features of ADHD, such as hyperactivity-impulsivity symptoms and emotional dysregulation. The findings point to self-medication for ADHD as a plausible explanation and suggest early diagnosis and treatment of ADHD as a preventive strategy against substance abuse.

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a life-span neuropsychiatric disorder, with core symptoms of inattention, hyperactivity, and impulsivity[1]. ADHD is caused by a multitude of additive and interactive genetic and environmental factors operating in a complex manner[2-4]. The prevalence of ADHD in the general adult population is estimated to be 3%-5%[5,6]. Furthermore, ADHD is a dimensional diagnosis in which attention deficits and hyperactivity-impulsivity may appear in various degrees and combinations[7].

The co-occurrence of ADHD and substance use disorder (SUD), such as alcohol use disorder (AUD) or drug use disorder (DUD), has been studied in a variety of clinical and research settings. Overall, there is an earlier onset and elevated risk of SUD in people with ADHD[6,8-16], but the direction of causality, underlying mechanisms, and clinical implications of the strong association between ADHD and SUD are still unclear.

It is well documented that many patients with ADHD strive to regulate negative emotions[17-19]. They may be quick to anger, easily frustrated, and emotionally over-excitable, a symptom cluster defined as emotional dysregulation (ED)[20-22]. Although ED may be understood as a transdiagnostic factor[23], in the development of psychopathology[24] it appears to be specifically related to impulsivity[25]. ED is

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associated with SUD in children and adolescents[26] as well as in adults with ADHD[27]. The strong relationship between ADHD and ED[17-19] makes it challenging to determine which of them is mainly related to SUD.

The aim of the present study was to estimate the prevalence of AUD and DUD in a clinical sample of adults with ADHD, and to examine the association with ADHD symptom severity and ED.

MATERIALS AND METHODS

This was an observational cross-sectional clinical study.

Participants

The study sample consisted of adult patients, age ranging from 18 to 69, who fulfilled the criteria for ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (commonly referred to as the DSM-5)[1]. They were admitted to a private psychiatric clinic in Oslo, Norway, which specialized in psychiatric examinations and treatment of ADHD.

Recruitment was conducted between 2014 and 2018. ADHD was assessed using DIVA 2.0, the semi-structured Diagnostic Interview for Adult ADHD, second edition[28], which was performed by a psychiatrist for all patients included in the study. A clinical diagnosis of ADHD was established according to DSM-5[1]. During these years, 656 of the assessed patients fulfilled the diagnostic criteria of ADHD and were invited to participate in the study, of whom 65% were self-referred and 35% were referred by healthcare practitioners. None of the participants were using prescribed stimulant medication prior to study inclusion.

Of the 656 patients (351 men and 305 women) with ADHD, 585 (89.2%) gave written informed consent to participate in the study. There were no exclusion criteria. The study was approved by the Regional Medical Ethics Committee, South-East Norway, 2015/426. Assessments were carried out in accordance with ethical standards and the principals of the Declaration of Helsinki.

Measures

The age of the participants was recorded as their numbers of lived-years when entering the study. Gender was recorded as women (scored as 0) and men (scored as 1) from the information revealed by the participant. Sociodemographic information included: If the participant was married or cohabiting, scored as 1, and if not, scored as 0; If the participant was living with children, inclusive partial custody, scored as 1, and if not (even though having children somewhere else), scored as 0; Educational level, categorized by the number of years in education, with 12 years or less scored as 1, 13-15 years scored as 2, or more than 15 years scored as 3; and, work participation, which was defined as "yes" and scored as 1, if work was reported as the main source of income, and if not was scored as 0.

AUD and DUD were diagnosed using the specific module of the Mini International Neuropsychiatric Interview (MINI), Norwegian Translation Version 6.0.0, according to DSM-IV criteria[29,30]. Dependence and abuse were merged into "use" disorder, as in MINI version 7.0/DSM-5, and questions were both restricted to the last 12-mo and related to lifetime prevalence. The presence of AUD was scored as 1, and absence as 0. The presence of DUD was scored as 1, and the absence as 0. ADHD symptom severity was measured using the Adult ADHD Self Report Scale (ASRS) Symptom Check List, v1.1 by the World Health Organization 2007. The ASRS is a reliable and valid screening instrument for evaluating ADHD in adults[31]. This 18-item version yields a score ranging from 0 to 72 points. We recorded subdivisions of the ASRS questionnaire, as inattentive items (item 1-4 and 7-11) and hyperactive/impulsivity items (item 5, 6, and 12-18) separately[32].

ED was assessed by questionnaire with 8 items from the 99-item Current Behavior Scale - Self Report questionnaire[33-35]. The 8 items were: 1: Quick to get angry or become upset; 2: Easily frustrated; 3: Overreact emotionally; 4: Easily excited by activities going on around me; 5: Lose my temper; 6: Argue with others; 7: Am touchy or easily annoyed by others; and 8: Am angry or resentful. The items were scored as never or rarely (0), sometimes (1), often (2), or very often (3). This yielded a total ED score ranging from 0 to 24.

Procedure

The data were collected during routine assessment in an outpatient clinic. Afterwards, the patients were asked if they approved the use of their clinical information in an anonymous form as statistic material for this clinical trial. They gave their written informed consent to participate in the study after the examination.

Statistical analysis

We performed χ^2 tests or *t*-tests to compare sociodemographic characteristics between women and men. We used logistic regression analyses to examine associations between AUDs and DUDs as dependent variables and ADHD symptom severity and ED as independent variables. All tests were two-tailed. Because of our two hypotheses, we used multiple test correction according to Bonferroni, considering differences significant if $P < 0.025$. There were no missing data. All statistical analyses were carried out using the software package IBM 2016 SPSS version 22[36].

RESULTS

Prevalence rates

Table 1 shows the sociodemographic and clinical characteristics of the men ($n = 317$) and women ($n = 268$) in the study. More women than men were living with children and women reported higher levels of ADHD symptoms and ED compared to men. Table 2 shows the 12-mo prevalence and lifetime prevalence of AUD and DUD in men and women. Men had a significantly higher prevalence of both AUD and DUD compared to women. The prevalence of DUD was more than twice the prevalence of AUD for both sexes.

Prevalence of different drugs

In the total sample, 162 (27.7%) of the participants had a history of lifetime DUD related to amphetamine ($n = 112$, 69.1%), cannabis ($n = 100$, 61.7%), cocaine or ecstasy ($n = 43$, 26.5%), benzodiazepines ($n = 43$, 26.5%), heroin or other opioids ($n = 17$, 10.5%), and unspecified drugs ($n = 26$, 16.0%).

Associations whit ADHD symptoms and ED

Tables 3 and 4 show associations between lifetime SUD and clinical characteristics, including hyperactivity-impulsivity and ED. Lifetime AUD was not significantly associated with the levels of ADHD symptoms or ED when adjusted for gender and age (Table 3). Lifetime DUD, on the other hand, was significantly associated with both hyperactivity-impulsivity and ED (Table 4).

DISCUSSION

In our clinical sample of adults with ADHD, we observed a 12-mo prevalence of 5.3% for AUD and 13.7% for DUD. The lifetime prevalence was 12.0% for AUD and 27.7% for DUD. All prevalence rates were higher for men than for women.

The 12-mo prevalence of AUD was similar to the general population prevalence reported in Norway and the United States[37-39]. In contrast, the 12-mo prevalence of DUD was considerably higher than the United States (3.9%)[40] and European (3.0%) estimated prevalences of DUD in the general population[38]. A similar pattern was found for lifetime prevalence of AUD and DUD. While the lifetime prevalence of AUD in our study was lower than that in the general Norwegian or United States population[37-39], the lifetime prevalence of DUD was considerably higher than what has been found in the Norwegian population[41,42].

Our findings demonstrate the need to distinguish between different types of SUD to understand comorbidity in patients with ADHD. The finding that DUD, in contrast to AUD, was far more prevalent than in the general population, as well as our findings that DUD but not AUD was associated with increased ED and ADHD symptom severity, questions previous statements that ADHD is strongly associated with SUD in general[13,14] or that the ADHD symptom severity is associated with increased risk for all kinds of SUD outcomes[16]. According to our findings, there appears to be a significant difference between the risk of AUD and DUD in people with ADHD, at least in this Norwegian patient population.

Table 1 Demographic characteristics, attention-deficit hyperactivity disorder symptom severity, and emotional dysregulation in 585 adult patients diagnosed with attention-deficit hyperactivity disorder in a psychiatric clinic specialized in examination and treatment of attention-deficit hyperactivity disorder

	Men, *n* = 317	Women, *n* = 268	All patients, *n* = 585
Age in years, mean ± SD	36.2 (11.5)	37.5 (11.2)	36.8 (11.4)
Range	18-67	18-69	18-69
Married or cohabitant	143 (45.1)	107 (39.9)	250 (42.7)
Living with children	110 (34.7)	117 (43.7)[a]	227 (38.8)
Years of education: ≤ 12	172 (54.3)	129 (48.1)	301 (51.5)
13-15	121 (38.2)	108 (40.3)	229 (39.1)
> 15	24 (7.6)	31 (11.6)	55 (9.4)
Work participation	193 (60.9)	149 (55.6)	342 (58.5)
ADHD symptom severity[1], mean ± SD	50.4 (9.5)	52.3 (9.5)[b]	51.4 (9.5)
Inattention, mean ± SD	27.0 (4.6)	27.8 (4.9)[a]	27.4 (4.7)
Impulsivity-hyperactivity, mean ± SD	23.3 (6.6)	24.7 (6.5)[b]	24.0 (6.6)
Emotional dysregulation[2], mean ± SD	11.0 (5.6)	13.4 (5.3)[c]	12.1 (5.6)

When others not specified, figures are given as numbers (percentage).
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$; women compared with men.
[1]Attention-deficit hyperactivity disorder (ADHD) symptom severity was assessed by the Adult ADHD Self Report Scale.
[2]Emotional dysregulation was assessed by 8 items from the Current Behavior Scale - Self Report questionnaire. SD: Standard deviation.

Table 2 Prevalences of alcohol or drug use disorders in 585 adult patients diagnosed with attention-deficit hyperactivity disorder in a psychiatric clinic specialized in examination and treatment of attention-deficit hyperactivity disorder

	Men, *n* = 317	Women, *n* = 268	All patients, *n* = 585
AUD			
- 12-mo	24(7.6)	7 (2.6)[b]	31 (5.3)
- Lifetime	47 (14.8)	23 (8.6)[a]	70 (12.0)
DUD			
- 12-mo	55 (17.4)	25 (9.1)[b]	80 (13.7)
- Lifetime	103 (32.5)	59 (22.0)[b]	162 (27.7)
AUD or DUD			
- 12-mo	67 (21.1)	29 (10.8)[b]	96 (16.4)
- Lifetime	114 (36.0)	65 (24.3)[b]	179 (30.6)

[a]$P < 0.05$.
[b]$P < 0.01$; women compared with men (χ^2). Figures are given in numbers (percentage). AUS: Alcohol use disorder; DUD: Drug use disorder.

Several factors can help explain this. First, genome-wide association studies have shown strong genetic correlations between ADHD and DUD[43,44], while some genetic factors contributing to the risk of developing AUD are negatively correlated with ADHD[45]. Second, there may be some shared environmental determinants for ADHD and DUD[44] — for example, maternal DUD[46]. Third, drug dependence, especially the misuse of amphetamine and cannabis, has been suggested to be a result of self-medication related to ADHD symptoms[47-49], which corresponds to the fact that amphetamine and cannabis were the preferred drugs for abuse in our study.

The higher prevalence rates of AUD and DUD in men compared to women are in accordance with gender differences in the general population[37-40]. In line with others,

Table 3 Associations between age, gender, attention-deficit hyperactivity disorder relevant clinical characteristics, and outcome of lifetime alcohol use disorder in a clinical sample of 585 adult attention-deficit hyperactivity disorder patients, non-adjusted and adjusted analysis

	Non-adjusted			Adjusted		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age, increasing in 10 yr	1.32	1.06-1.64	0.013	1.32	1.05-1,64	0.016
Gender, men *vs* women	1.94	1.14-3.31	0.015	2.19	1.27-3.77	0.005
Inattentive	1.03	0.98-1.09	0.27	1.01	0.95-1.07	0.82
Hyperactivity- impulsivity	1.05	1.01-1.09	0.027	1.03	0.98-1.08	0.24
Emotional dysregulation	1.05	1.00-1.09	0.06	1.04	0.98-1.10	0.16

CI: Confidence interval; OR: Odds ratio.

Table 4 Associations between age, gender, attention-deficit hyperactivity disorder relevant clinical characteristics, and outcome of lifetime drug use disorder in a clinical sample of 585 adult attention-deficit hyperactivity disorder patients, non-adjusted and adjusted analysis

	Non-adjusted			Adjusted		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age, increasing in 10 yr	1.10	0.94-1.29	0.24	1.08	0.92-1.27	0.36
Gender, men *vs* women	1.71	1.18-2.49	0.005	2.01	1.36-2.97	< 0.001
Inattentive	1.02	0.97-1.05	0.77	0.97	0.93-1.02	0.21
Hyperactivity-impulsivity	1.04	1.02-1.07	0.003	1.04	1.01-1.08	0.021
Emotional dysregulation	1.05	1.01-1.08	0.006	1.05	1.01-1.09	0.019

CI: Confidence interval; OR: Odds ratio.

we found that women reported higher levels of hyperactivity-impulsivity[50] and ED[51] compared with men.

Our observation that DUD was associated with higher ED is consistent with findings that ED in general increases the risk of developing and maintaining drug addiction[52]. DUD typically appears later in life than ADHD and ED, suggesting that DUD is modified by ADHD and ED, rather than *vice versa*. Nevertheless, it is possible that DUD may reinforce the symptoms of both ADHD and ED.

Methodological considerations

Patients attending a private and not governmental-funded ADHD clinic may not be representative for patients with ADHD in general. They may have a higher socio-economic status and be less impaired compared to those in public outpatient clinics or hospitals. Also, the prevalence of morbidity may not be representative of the total ADHD patient population. Still, the reported comorbidity prevalence rates in our study were similar to recently reported prevalences for the total Norwegian population[12]. Finally, the cross-sectional design places strong limitations on interpretations of causal relationships.

CONCLUSION

In conclusion, in this study of adult ADHD patients, we found a much higher prevalence of DUD than what has been reported in general populations. DUD was independently associated with both higher symptom levels of hyperactivity-impulsivity and ED. Thus, a co-morbid DUD should be considered in adult ADHD patients, particularly in males and among individuals with high levels of hyperactive-impulsive ADHD core symptoms or ED. The causal mechanisms of the relationship

between ADHD and DUD are not known, but self-medication for hyperactivity-impulsivity and ED is one possibility. Thus, early recognition and targeted interventions may be necessary to prevent the negative consequences of ADHD.

ARTICLE HIGHLIGHTS

Research background

The co-occurrence of attention-deficit hyperactivity disorder (ADHD) and substance use disorders, such as alcohol use disorder (AUD) and drug use disorder (DUD), has been studied in a variety of clinical and research settings. It is still unclear whether an increased risk of abuse or dependence applies to all forms of substance use to the same extent.

Research motivation

We have yet to fully understand the magnitude and nature of substance use among the adult population with ADHD. By obtaining more knowledge about the prevalence of AUD and DUD in adults with ADHD and the associations with clinical features of ADHD, this information can lead to hypotheses as to why some people with ADHD are at greater risk of developing substance use disorder.

Research objectives

To estimate the prevalence of AUD and DUD in adults with ADHD, and to estimate the associations with ADHD symptom severity and emotional dysregulation.

Research methods

This was an observational cross-sectional clinical study with a study sample consisting of 585 adult ADHD patients, who were admitted to a private psychiatric outpatient clinic over a 5-year period. ADHD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria. AUD and DUD were diagnosed using the Mini International Neuropsychiatric Interview. ADHD severity was assessed by the Adult ADHD Self Report Scale. Emotional dysregulation was assessed by the 8-item version of Barkley's Current Behavior Scale - Self Report.

Research results

The 12-mo prevalences of AUD and DUD were 5.3% and 13.7%, respectively. The lifetime prevalence was 12.0% for AUD and 27.7% for DUD. A history of DUD but not AUD was positively associated with hyperactivity-impulsivity ADHD core symptoms, as well as emotional dysregulation.

Research conclusions

Compared to findings in the normal population, adult ADHD patients had much higher prevalence of past or current DUD but not AUD. DUD was particularly related to amphetamine and cannabis. Associations of DUD with clinical features of ADHD point to self-medication of ADHD as a possible causative factor and suggest early diagnosis and treatment of ADHD as a preventive strategy against substance abuse.

Research perspectives

Future research should be supplemented by longitudinal studies of children and adolescents with ADHD to investigate who develops substance use disorders. The effect of early ADHD treatment on substance abuse can be investigated by intervention studies.

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ORIGINAL ARTICLE

Observational Study

Delirium, insulin-like growth factor I, growth hormone in older inpatients

Dimitrios Adamis, Iulian Coada, Piet Eikelenboom, Che-Sheng Chu, Karen Finn, Vincent Melvin, John Williams, David James Meagher, Geraldine McCarthy

ORCID number: Dimitrios Adamis 0000-0003-1315-1695; Iulian Coada 0000-0002-4212-375X; Piet Eikelenboom 0000-0001-7767-1732; Che-Sheng Chu 0000-0002-6911-1839; Karen Finn 0000-0002-5631-9710; Vincent Melvin 0000-0002-6429-5341; John Williams 0000-0001-9813-6691; David James Meagher 0000-0001-8324-8017; Geraldine McCarthy 0000-0002-1312-0998.

Author contributions: Adamis D was involved in the conceptualization of the project, data curation, statistical analysis, supervision of the project, writing-original draft; Coada I was involved in data entry, curation, writing-original draft; Eikelenboom P was involved in the conceptualization, supervision of the project, writing-original draft; Chu C was involved in the conceptualization, supervision, and writing-original draft; Finn K was involved in the biochemical analysis, data entry, data curation, writing-original draft; Melvin V was involved in the clinical data collection, data entry and curation, writing-original draft; Williams J was involved in the conceptualization, biochemical analysis, supervision, funding acquisition and writing the original draft; Meagher D was involved in

Dimitrios Adamis, Iulian Coada, Vincent Melvin, Geraldine McCarthy, Department of Psychiatry, Sligo/Leitrim Mental Health Services, Sligo F91 CD34, Ireland

Dimitrios Adamis, Department of Psychiatry, Research and Academic Institute of Athens, Athens 11742, Greece

Dimitrios Adamis, David James Meagher, Department of Psychiatry, University Hospital Limerick, Limerick V94 F858, Ireland

Piet Eikelenboom, Department of Psychiatry, GGZinGeest and VuMC, Amsterdam 1081 HV, the Netherlands

Che-Sheng Chu, Department of Psychiatry and Center for Geriatric and Gerontology, Kaohsiung Veterans General Hospital, Kaohsiung 81362, Taiwan

Karen Finn, Department of Biopharmaceutical and Medical Science, School of Science and Computing, Galway-Mayo Institute of Technology, Galway H91 T8NW, Ireland

John Williams, Department of Pathology, Sligo University Hospital, Sligo F91 H684, Ireland

Corresponding author: Dimitrios Adamis, MD, MSc, Academic Research, Department of Psychiatry, Sligo/Leitrim Mental Health Services, Clarion Road, Sligo F91 CD34, Ireland. dimaadamis@yahoo.com

Abstract

BACKGROUND

Delirium is a common disorder in elderly medical inpatients with serious adverse outcomes and is characterized by sudden onset, disturbance in attention, awareness, consciousness and cognition, and often with behavioural disturbances. Central to understanding delirium, is understanding mechanisms by which body and brain wellbeing are linked and in particular how brain responses to bodily homeostatic stress is mediated. A number of studies have investigated the relationship between insulin-like growth factor I (IGF-I) and delirium in medically ill hospitalised patients with conflicting results. However, none have investigated growth hormone (GH) which is related to IGF-I *via* negative feedback.

AIM

the conceptualization, supervision, and writing the original draft; McCarthy G was involved in the conceptualization, supervision, funding acquisition and writing the original draft; all authors have contributed read and approve the final manuscript.

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To investigate the relationship between serum levels of IGF-I and GH, and the occurrence of delirium.

METHODS

Prospective, longitudinal, observational study. Consecutive elderly inpatients (aged 70+), were assessed twice weekly with Montreal cognitive assessment (MoCA), Confusion assessment method (CAM), Acute Physiology and Chronic Health Evaluation II. Delirium was defined using CAM. Previous history of dementia was evaluated with the Informant Questionnaire on Cognitive Decline in the Elderly. IGF-I and GH levels were estimated with the ELISA method. Generalized estimating equations (GEE) model was applied for the first five assessments to analyze those longitudinal data.

RESULTS

The sample consisted of 198 participants (mean age 80.63 ± 6.81; range 70-97). Of these 92 (46.5%) were females. Eighty six (43.4%) were identified with a history of dementia. Incident or prevalent delirium during hospitalisation was identified with CAM in 40 participants (20.2%). Evaluation of missing values with Little's MCAR test indicated that they were missing completely at random (MCAR χ^2 = 12.24, *u*: 9, *P* = 0.20). Using GEE for the analysis we found that low MoCA scores, low levels of IGF-I and high levels of GH were significantly associated with any delirium (prevalence, incident, or fluctuating , during the study period (Wald χ^2 = 12.231; *u*: 1, *P* < 0.001, Wald χ^2 = 7.196, *u*: 1, *P* = 0.007, Wald χ^2 = 6.210; : *u:* 1, *P* = 0.013 respectively).

CONCLUSION

The results show that low levels of IGF-I, high levels of GH and low scores in cognition are independently associated with the occurrence of any delirium during the hospitalisation of medically ill older people. The results of the study supports the hypothesis that deficits in the immunoreactivity of the brain (low cerebral reserve) may be associated with delirium.

Key Words: Delirium; Pathophysiology; Insulin-like growth factor-I; Growth hormone; Older people; Physical illness; Cognition; Old age psychiatry

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Core Tip: The present work investigates the association of serum levels of insulin-like growth factor I (IGF-I) and growth hormone (GH) with delirium presence in older medically ill hospitalised people. We found, in accordance with previous studies, that low levels of serum IGF-I and high levels of GH together with cognitive deficits are associated with the occurrence of delirium.

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INTRODUCTION

Delirium is a syndrome which often presented with sudden onset, and disorders of the cognitive, consciousness, motor, affective, and perceptual domains. Those disturbances often are fluctuated[1]. It also manifested with different motor subtypes like hyperactive, hypoactive or mixed states[2].

Delirium is a common disorder in elderly medical inpatients. In Irish hospitals the point prevalence of delirium is estimated around 20%[3]. Higher rates are reported among patients in palliative and intensive care settings[3,4]. Delirium has severe bad consequences like, delays in hospital discharges increased hospital budgets[5], higher rates of institutionalisation[6], and perhaps increased mortality[7]. The old-fashioned

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concept of delirium as a brief, transient, and highly reversible condition is no longer supported by longitudinal studies. Accumulating evidence support that delirium is associated with persistent cognitive and functional problems[8,9] and delirium may be an accelerating and possibly causal factor in the development of dementia[10]. Notably, these adverse outcomes are independent of the severity of physical illness that cause delirium. Despite the understanding that delirium is caused by physical illness, it is not clear yet how those physical causes without direct connection with brain, can produce such a consistent complex neuropsychiatric picture as found in delirium. Thus, the pathophysiology of delirium remains unclear and many pathophysiological mechanisms have been hypothesised and suggested but none yet proved[5,11].

Delirium often occurs in the context of infectious illness and the external administration of cytokines in a number of medical illness for therapeutic reasons, can results to delirium. Thus, in an effort to clarify the pathophysiology of delirium a number of studies have investigated cytokine levels, but the results are conflicted and inconclusive[12]. However, from our previous work[13] we found that low circulating levels of neuroprotective factors of IGF-1 and interleukin-1 receptor antagonist (IL-1RA) were connected with delirium. Although there are few studies with firm conclusions about the role of cytokines in delirium, a hypothesis in which we work is that cerebral deficits may be the reason for the occurrence of delirium. This has led our research group to work on the general hypothesis that delirium is associated with already existed deficits in the brain regarding the immunoreactivity and the readiness to respond to the external "insult" (*e.g.*, physical illness). Low levels of neuroprotective factors may possibly explain the onset of delirium rather than the actual trigger or "insult" factor. This can explain the observations that the severity of physical illness is not a risk factor for delirium at least in older populations[14]. One of those neuroprotective factors which has been investigated in delirium is the IGF-I.

IGF-I is regulate the body growth and metabolism but involves also in different brain functions. Circulating IGF-I is produced mainly from the liver but it can be produced by any cell type. The receptors of IGF-I are on almost all different cells including brain and have neuroprotective effects[15,16]. In addition IGF-I receptors play significant role in the integrity and regulation of blood-brain barrier, they have high expression in the cells that constitute it and they facilitate the access of serum IGF-I to entry into the brain[17].

In the Central Nervous System the IGF-I is produced by neurons and glial cells[18] and plays an extensive role in the development, plasticity and survival of neurons. IGF-I involves in the production of neurotransmitters, blocks apoptosis in damaged neurons, and thus has effects on cognition and cognitive decline during ageing or in other neurocognitive disorders like dementia and delirium[16,19-21].

However, IGF-I is not independent. The secretion of IGF-I is under the control of growth hormone (GH) which is called the GH/IGF-1 axis. GH is pleiotropic hormone which regulates many functions like feeding, growth, metabolism, reproduction, and immune system function. The secretion of GH is stimulated by the GHRH from the hypothalamus. GH secretion is also influenced by IGF-I, which involves a negative feedback mechanism[22,23].

Higher levels of GH are associated with risen levels IGF-I until a certain point where a plateau is reached[24]. It has been reported[25] that cerebrospinal levels of somatostatin (Growth hormone Inhibiting hormone) are significantly lower during delirium but and later at follow-up. This does not indicate a directly link between delirium and GH, but indicates a disturbed GH/IGF-1 axis in delirium. In the same line, in patients admitted to the intensive care unit it was found that low levels of IGF-I were correlated with high levels of GH[26]. In addition, a study[27] reported that administration of human GH in aged women following hip operation had increased IGF-I levels. Therefore, until now we do not know the way of the interaction of GH and IGF-I during delirium. In our previous review we have identified a lack of research work in relation to GH in studies which investigated IGF-I and delirium[12].

Nevertheless, a number of studies have investigated the relationship of IGF-I with delirium in medically ill hospitalised patients as well as in patients undergoing surgery with conflicting results. A resent meta-analysis[28] showed that there are indications of an association of IGF-1 and delirium but the authors also calling for further research into this area.

Given the previous studies and the new updates we carried out a new study in older medically ill hospitalised patients with the aim to find out the relationship of the circulating levels of IGF-I and GH to the delirium (in both prevalent and incident).

MATERIALS AND METHODS

The present study was designed as a pragmatic prospective, longitudinal study. The study was carried out in a University Hospital in Sligo in the North-West of Ireland. The inclusion criteria were: (1) Consecutive admitted patients in the elderly medical wards; and (2) To be 70 years old and above. Exclusion criteria were (1) Patients who were readmitted and had already participate in the study; (2) Patients intubated or with aphasia; (3) Patients in a terminal stage of illness; and (4) Patients unable to speak English. A time frame of 72 h since admission was in place for the assessment of the eligibility for recruitment and the recruitment of participants.

Procedure

Those patients who fulfilled the inclusion criteria and consented had an assessment at first day. Then seven more assessments were followed in a regular space of 3 ± 1 d if they were still hospitalised and alive. The maximum number of assessment was eight. Non-fasting blood was withdrawn the same days of the assessments. Bloods were centrifuged within ten minutes and then stored at -70 °C until analysis. Levels of IGF-I and GH were estimated with the ELISA method. Levels of IGF-I are measured in ng/ml and levels of GH in pg/mL.

Assessments and scales

Demographic data were collected from the computer of the hospital database. In addition at each time the following measurements/scales were administered.

Cognitive scale

The Montreal Cognitive Assessment (MoCA)[29] have been used for assessment of cognition. The maximum score in MoCA is 30 which indicates an intact cognition. In participants who were unable to complete all the sections due to a physical disability (*e.g.*, visual impairment) MoCA results were standardized to give a maximum score of 30. To complete the MoCA it takes about 12-15 min.

Assessment/scale for delirium

The presence/absence of delirium was assessed with the CAM scale/algorithm[30]. The CAM is based in DSM-IIIR criteria for delirium. It asses four "cardinal" criteria for delirium.

Physical illness

To assess the severity of the underling physical illness the Acute Physiology and Chronic Health Evaluation II (APACHE-II)[31] (Acute Physiology and Chronic Health Evaluation II) and the APS subscale (Acute Physiology Score) were used. Higher scores in both scales indicate more illness severity.

Diagnosis of previous history of dementia

Pre-existing dementia was assessed with two ways. First if it was documented clearly according to DSM-IV diagnostic criteria or if not the Short Informant Questionnaire of Cognitive Decline was used by interviewing the nearest relative. The cut-off point of ≥ 3.5[32] was used to define pre-existing dementia.

Ethical considerations

Informed consent was in writing using an earlier described method[33]. A separate consent in writing was asked for phlebotomy. The Sligo University Hospital Research Ethics Committee has graded Ethical approval for the project.

Statistical analysis

SPSS v23 was used for the analysis of the data. Continuous variables were presented as mean ± SD and categorical as counts and percentages. The Generalized Estimating Equations (GEE) method was used to analyse the effects of independent variables on delirium. GEE adjusts for correlations due to repeated assessments of each participant[34]. Because the dependent variable (delirium/no delirium) was binary the binominal distribution was used. To evaluate the fit of the model the Corrected Quasi Likelihood under Independence Model Criterion (QICC) value was used, (lower value – better fit). Because there were many missing values in the last 3 assessments (drop-outs) only the first 5 will be entered to the model.

RESULTS

Description of the sample

A total of 198 participants were analysed. The mean age of the participants was 80.63 ± 6.81; range 70-97. Of these 106 (53.5%) were males. Previous history of dementia was found in eighty six (43.4%). The characteristics of the two groups (delirium/ no delirium) at each of the five assessments, including means and standard deviations of the scales MoCA, and APACHE II scores, and IGF-I and GH levels at each assessment are shown in Table 1. Figure 1 shows the mean levels of IGF-I and GH across the assessments for those with and without delirium.

Evaluation of missing data

This was done by using the Little's MCAR test. The results of the test was not significant (MCAR, χ^2 = 12.24, *u:* 9, P = 0.20) which indicates that the missing values were missing completely at random

Longitudinal analysis: GEE model

Here we examined the effects of the independent variables age, gender, previous history of dementia (binary yes/no), APACHE II, MoCA scores, and the levels of IGF-I and GH on the dependent variable delirium/no delirium (binary). The most parsimonious model (lowest QICC value) is shown in Table 2.

The results from the Table 2 shows that those with any delirium during the hospitalisation had significantly lower scores in the MoCA scale, lower levels of IGF-I and higher levels of GH compared to those without delirium. None of the other examined variables (age, gender, previous history of dementia or severity of physical illness (APACHE II) had any significant effect in the presence or absence of delirium as it was defined with CAM.

DISCUSSION

First of all, the results show that deficits in cognition as measured with the MoCA, are a significant independent predictor for the occurrence of any delirium (prevalent, incident, or fluctuating). This result is constantly found in all the studies which investigate delirium because disturbance in cognition is a central feature of delirium. Therefore this is a result which was expected. In addition the severity of the physical illness (as measured with APACHE II), previous history of dementia, and age did not have any effect on delirium. Severity of physical illness again is an expected finding since in our previous studies we did not find any effect and thus we generate the hypothesis that it is not the severity of insult that is important for causing the delirium but the reduced neuroprotection of the brain. Besides the lack of effect of age and previous history of dementia is easily explained by the more powerful predictor, scores in the MoCA.

Regarding the IGF-I, the results of the present study is in accordance with our previous study[13] in which we use similar methodology and longitudinal design but in a different population, different hospital and in a different country and also confirmed that low levels of circulating IGF-I are significantly linked with any delirium (incident or prevalence). Similar results have been reported form other research groups[35-39], but not from all[40-43]. However a resent meta-analysis[28] showed that lower levels of circulating IGF-I are associated with higher rates of delirium among older patients. There are many reasons for those discrepancies among the studies, (see also[28]). First of all different populations were studied. Some studies include populations with pre-existing dementia (*e.g.*, the present study) while others excluded them[41,42]. A second reason perhaps is the setting where the study is conducted and the sample. Some of the studies were conducted in medical wards where the sample include populations with mainly medical illness while others in surgical wards in patients before and after surgery. Perhaps surgery is another stressor and perhaps pathophysiology which leads to delirium in those patients is different despite the end product being the same. In addition those studies in surgery wards have examined patients before and immediately after the surgery for delirium. However, it has been suggested that perhaps different mechanisms are underline the delirium that developed in the first 24 hours after surgery and in the delirium that developed the next one to three days after surgery[44]. Finally one important reason which can explain those discrepancies is the different scales/measurements/criteria that have been applied to define delirium. It has been shown that applying different criteria for delirium is influence significantly

Table 1 Cases of delirium and no delirium (according to confusion assessment method) with the scores (mean ± SD) of the Montreal cognitive assessment, acute physiology and chronic health evaluation II and growth hormone, insulin-like growth factor I levels at each assessment point

Assessment	CAM (*n*)		MoCA	APACHE II	IGF-I (ng/mL)	GH (pg/mL)
1	No delirium (173)	mean ± SD	11.38 ± 7.90	8.59 ± 3.68	61.32 ± 22.95	503.95 ± 743.05
		Valid, *n*	168	173	68	68
	Delirium (24)	mean ± SD	3.78 ± 2.76	9.00 ± 3.86	45.88 ± 14.66	693.89 ± 462.15
		Valid, *n*	23	24	8	8
2	No delirium (141)	mean ± SD	10.42 ± 8.23	8.69 ± 3.69	53.93 ± 18.57	434.22 ± 561.88
		Valid, *n*	134	140	49	49
	Delirium (11)	mean ± SD	3.67 ± 3.43	11.00 ± 5.20	41.78 ± 13.98	652.14 ± 346.98
		Valid, *n*	9	11	5	5
3	No delirium (90)	mean ± SD	9.27 ± 7.58	8.77 ± 3.67	60.66 ± 18.88	487.98 ± 648.70
		Valid, *n*	84	88	30	30
	Delirium (13)	mean ± SD	3.90 ± 2.51	10.38 ± 3.69	58.29 ± 14.60	487.25 ± 507.84
		Valid, *n*	10	13	5	5
4	No delirium (58)	mean ± SD	10.63 ± 7.44	8.79 ± 3.55	61.97 ± 22.70	622.00 ± 790.09
		Valid, *n*	56	58	18	18
	Delirium (8)	mean ± SD	6.00 ± 1.83	9.00 ± 2.67	41.43 ± 8.13	577.94 ± 200.90
		Valid, *n*	7	8	2	2
5	No delirium (46)	mean ± SD	8.70 ± 7.20	8.80 ± 3.28	53.70 ± 14.37	288.27 ± 245.51
		Valid, *n*	43	46	11	11
	Delirium (6)	mean ± SD	2.33 ± 1.03	9.50 ± 3.33	42.62 ± 2.42	924.34 ± 677.88
		Valid, *n*	6	6	4	4

CAM: Confusion assessment method; MoCA: Montreal cognitive assessment; APACHE II: Acute physiology and chronic health evaluation II; IGF-I: Insulin-like growth factor I; GH: Growth hormone.

Table 2 Generalized estimating equations model and parameter estimates of the significant variables on delirium status

Parameter estimates							
Parameter	B	SE	95%CI		Hypothesis test		
			Lower	Upper	Wald χ^2	*u*	Sig.
GH (pg/ml)	-0.0011[1]	0.0002	-0.001	0	6.21	1	0.013
IGF-1 (ng/ml)	0.02	0.0074	0.005	0.034	7.196	1	0.007
MoCA	0.205	0.0586	0.09	0.32	12.231	1	< 0.001

[1]The sign (-) shows the direction of the relationship. Reference status: No delirium. GH: Growth hormone; IGF-I: Insulin-like growth factor I; MoCA: Montreal cognitive assessment.

the rates and diagnosis of delirium and there is extensive discrepancy between the actual cases defined by each different system[45-48].

Furthermore, the present study for first time shows that GH is an important factor in the pathogenesis of delirium. However, because IGF-I and GH are correlated with a negative loop feedback we do not know which of them is more important in the pathogenesis of delirium. From the present study what we can conclude is that the somatotropic axis (IGF-I/GH) is disturbed during the delirium phase compared to those without delirium. Low IGF-I and high GH levels are related to delirium. To the best of our knowledge no previous studies have investigated the IGF-I/GH axis.

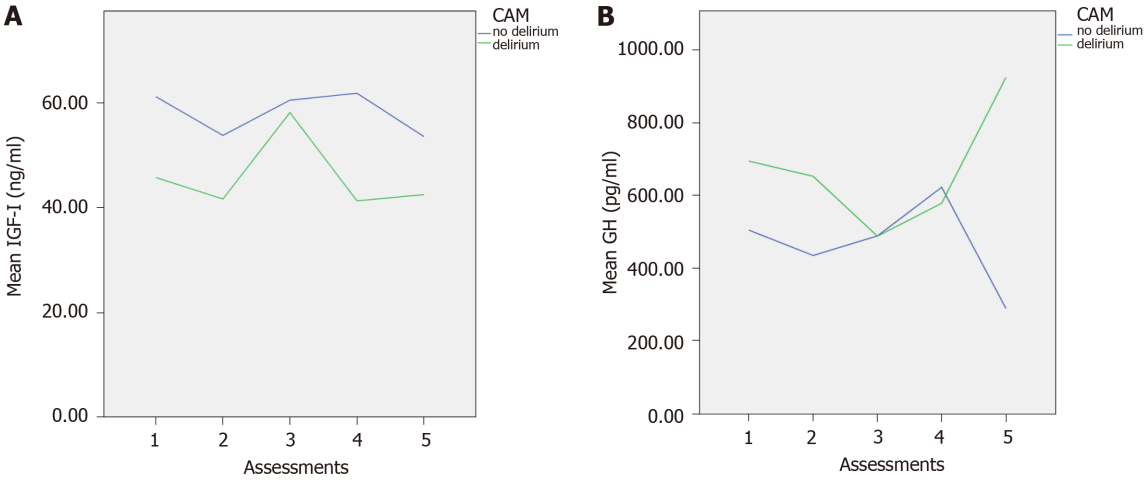


Figure 1 Means of insulin-like growth factor I (A) and growth hormone (B) across the assessments of delirium and no delirium. IGF-I: Insulin-like growth factor I; GH: Growth hormone; CAM: Confusion assessment method.

Therefore we attempt to explain our hypothesis further.

The secretion of GH is age related and a decline of GH started between the ages of 18 to 25 years. This decrease of the GH concentration in the periphery is accompanied by a gradual decline of IGF-I as well[27,49]. In addition, lower levels of GH are correlated with frailty[27] and exogenous administration of GH can increase energy, and improve mood, concentration, and memory. Those improvements in cognition may are the results of a direct effect of GH in the brain[50,51]. Therefore, perhaps the increased levels of GH reflect a compensatory mechanism in the brain to recover through a direct effect of GH. However, this does not explain the low levels of IGF-I which interestingly have been proven to protect neurons directly[52]. Experimental studies in animals have shown that after administration of IGF-I in brain injuries there was an improvement in the outcomes (regarding behaviour and cognition)[53]. IGF-I has also been proposed as a treatment for Alzheimer's disease because it play a crucial role in tau pathway and acetyl-choline which both connected with the occurrence of delirium[54]. Therefore a direct effect of IGF-I is more likely than a direct effect of GH. In the same line a second explanation has been suggested that in acute inflammation situations there is a GH resistance because the body prevents growth and energy storage in an attempt to keep the homeostasis. In those situations of acute inflammation the levels of IGF-I reduced, regardless of the increase of GH[41,55].

Taken together those suggestions provide a likely explanation that in delirious states GH is increased because of the disturbed IGF-I / GH axis and the lack of inhibitory mechanism of IGF-I.

Whatever mechanism is involved we cannot conclude from this study and it is important to notice that we measure levels in the periphery which may or may not reflect the brain levels of IGF-I and GH. However, we can conclude that in delirium the IGF-I/GH axis is disturbed, and that low levels of IGF-I together with high levels of GH and impaired cognition are independently significant predictors of delirium.

Limitations of the study

An obvious and common limitation of those kinds of studies including the present is the small sample size. However, the drop-outs and missing data of the study were completely missing at random so no biases have introduced in the study. A second limitation of the study is the lack of generalizability. The results of this study apply only in medically ill older people and not in other populations. Perhaps similar studies are needed also in other populations like surgical patients. There are ongoing collaborative studies examined the role of serum factors in postoperative delirium. Surgery induced delirium is a good model to separate the predisposal factors (preoperative) from the precipitating factors (post-operative) in the occurrence of delirium. Furthermore, the strengths of his study are the longitudinal design and the statistical analysis accompanied the design. By having this design and analysis we have included all the deliria during hospitalisation (prevalence, incident, fluctuated, and persistent) compared with the non-delirium states (including never delirium during hospitalisation and recovered delirium) across the time in the entire examined population.

Implications of the study

As we noted above, further studies need to be done in different populations before we be asserted about the results. If the results are replicated in further studies this can lead to clinical trials for the treatment and / or prevention of delirium with small doses of IGF-I.

CONCLUSION

In conclusion, this study indicates that during delirium in older medically ill hospitalised patients the IGF-I/GH axis is disturbed but we do not know yet the mechanism behind it. However more studies are needed to confirm or disconfirm the above findings before we move further to clinical trials for treatment or prevention of delirium with small doses of IGF-I.

ARTICLE HIGHLIGHTS

Research background

Delirium is a common disorder in elderly medical inpatients, in surgical wards, and Intensive care units with serious adverse outcomes.

Research motivation

To understand delirium is important to understand the underline mechanisms by which body and brain are linked and how brain responses to bodily homeostatic stress is mediated. We have notice from our previous research work that the severity of physical illness is not a risk factor for delirium at least in older populations and perhaps delirium is associated with deficits in the immunoreactivity of the brain (low cerebral reserve). Low levels of neuroprotective factors may possibly explain the onset of delirium rather than the actual trigger or "insult" factor. A number of studies have investigated the relationship between Insulin-like growth factor I (IGF-I) and delirium with conflicting results. A relevant also factor is the Growth Hormone (GH) which is related to IGF-I *via* negative feedback. Therefore in the present study we included also the GH.

Research objectives

To investigate the relationship of the occurrence of delirium during hospitalisation (prevalent and incident) with the serum levels of IGF-I and GH.

Research methods

Observational, prospective, longitudinal study of older people who consecutively admitted to medical wards of a general hospital.

Research results

We found that low cognitive function, low levels of IGF-I and high levels of GH were significantly associated with any delirium (prevalence, incident, or fluctuating) during the study period.

Research conclusions

The involvement of GH in delirium is a new finding from the present study. Also the finding of the low levels of IGF-I and the association of delirium confirms some of the previous studies. Those findings together with the association of cognitive decline with delirium strength the primary hypotheses that low brain reserves are possible the predisposing factor for delirium. Those findings needs further replication in other studies and especially in surgical samples

Research perspectives

If the above findings are replicated in future studies then the next step is clinical trials with small doses of IGF-I for prevention of delirium.

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ABOUT COVER

Associate editor of *World Journal of Psychiatry*, Dr. Giuseppe Lanza is Senior Academic Researcher and Assistant Professor at the University of Catania (Italy). After graduation with honors in Medicine, he trained in the School of Neurology and was awarded the international PhD from the same University. From 2013 to 2018, he worked as Consultant Neurologist at the Oasi Research Institute–IRCCS in Troina (Italy), a World Health Organization (WHO) collaborating center. He has co-authored more than 130 publications in peer-reviewed journals and conferences and reviewed for several international journals. More recently, he obtained a Master of Science in Clinical Research and the National Scientific Qualification as Full Professor. His ongoing research interests involve the translational neurosciences, particularly the application of non-invasive brain stimulation techniques in the diagnosis and treatment of neurological and neuropsychiatric disorders. (L-Editor: Filipodia)

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REVIEW

Mechanisms of repetitive transcranial magnetic stimulation for anti-depression: Evidence from preclinical studies

Di Luan, Ming-Ge Zhao, Ya-Chen Shi, Ling Li, Yu-Jia Cao, Hai-Xia Feng, Zhi-Jun Zhang

ORCID number: Di Luan 0000-0002-8832-7555; Ming-Ge Zhao 0000-0001-7885-5250; Ya-Chen Shi 0000-0003-2241-9227; Ling Li 0000-0003-2073-2105; Yu-Jia Cao 0000-0003-0837-9214; Hai-Xia Feng 0000-0002-1718-0971; Zhi-Jun Zhang 0000-0001-5480-0888.

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Di Luan, Ya-Chen Shi, Ling Li, Yu-Jia Cao, Zhi-Jun Zhang, Department of Neurology, Affiliated Zhongda Hospital, Research Institution of Neuropsychiatry, School of Medicine, Southeast University, Nanjing 210009, Jiangsu Province, China

Ming-Ge Zhao, Hai-Xia Feng, Department of Nursing, School of Medicine, Southeast University, Nanjing 210009, Jiangsu Province, China

Zhi-Jun Zhang, Department of Psychology, Xinxiang Medical University, Xinxiang 453003, Henan Province, China

Zhi-Jun Zhang, Mental Health Center, Zhejiang University School of Medicine, Hangzhou 310013, Zhejiang province, China

Corresponding author: Zhi-Jun Zhang, MD, PhD, Doctor, Full Professor, Department of Neurology, Affiliated Zhongda Hospital, Research Institution of Neuropsychiatry, School of Medicine, Southeast University, No. 87 Dingjiaqiao, Nanjing 210009, Jiangsu Province, China. janemengzhang@vip.163.com

Abstract

This review summarizes the anti-depressant mechanisms of repetitive transcranial magnetic stimulation in preclinical studies, including anti-inflammatory effects mediated by activation of nuclear factor-E2-related factor 2 signaling pathway, anti-oxidative stress effects, enhancement of synaptic plasticity and neurogenesis *via* activation of the endocannabinoid system and brain derived neurotrophic factor signaling pathway, increasing the content of monoamine neurotransmitters *via* inhibition of Sirtuin 1/monoamine oxidase A signaling pathway, and reducing the activity of the hypothalamic-pituitary-adrenocortical axis. We also discuss the shortcomings of transcranial magnetic stimulation in preclinical studies such as inaccurate positioning, shallow depth of stimulation, and difficulty in elucidating the neural circuit mechanism up- and down-stream of the stimulation target brain region.

Key Words: Repetitive transcranial magnetic stimulation; Anti-depressant mechanisms; Nuclear factor-e2-related factor 2; Endocannabinoid system; Monoamine oxidase; Hypothalamic-pituitary-adrenocortical axis; Brain derived neurotrophic factor

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Core Tip: Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for major depressive disorder. This paper reviews the anti-depressant mechanisms of rTMS that have been found in preclinical studies in recent years and discusses the shortcomings of TMS in preclinical studies.

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INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and vagus nerve stimulation are three physical strategies that have been approved by the United States Food and Drug Administration for the treatment of major depressive disorder (MDD)[1]. Compared with ECT and vagus nerve stimulation, rTMS is more readily accepted by patients with MDD because it does not require anesthesia and minimally invasive surgery with fewer side effects.

Since rTMS is an effective treatment for MDD[2-6], understanding its anti-depressant mechanisms may help to deepen the understanding of depression. This paper focuses on preclinical studies, reviews the underlying mechanisms of rTMS in animal models of depressive-like behavior, and discusses the shortcomings and deficiencies of rTMS in preclinical studies. Preclinical studies have shown that rTMS plays an anti-depressant role through a variety of mechanisms with diverse signaling pathways (Table 1).

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ACTIVATES THE ANTI-INFLAMMATORY EFFECTS MEDIATED *VIA* THE NUCLEAR FACTOR-E2-RELATED FACTOR 2 SIGNALING PATHWAY

Inflammation is strongly associated with depression[7-10]. Patients with autoimmune and infectious diseases are more likely to develop depression[11]. Patients with aseptic inflammation in the brain (such as stroke) are more likely to be accompanied by depression[12]. There are few clinical studies on the effects of rTMS on immune inflammation in MDD patients. Langguth *et al*[13] reported the recurrence of rheumatoid arthritis in an elderly female patient with treatment-resistant depression (TRD) comorbid with rheumatoid arthritis after receiving 20 Hz (intensity, 90% motor threshold) rTMS. After the patient received rTMS, the peripheral C-reactive protein and interleukin-6 (IL-6) contents increased (from 6.7 mg/L to 25 mg/L and from 3.4 ng/L to 15 ng/L, respectively), indicating that rTMS enhanced the inflammatory response of the patient. In contrast, Zhao *et al*[14] recruited 58 elderly patients with TRD and 30 healthy controls. The levels of peripheral IL-1β and tumor necrosis factor α (TNFα) in the patients were higher than those in healthy controls. Compared with the non-rTMS treated group, peripheral IL-1β and TNFα levels were markedly reduced in patients who were continuously treated with 10 Hz (intensity, 80 % motor threshold) rTMS for 4 wk. In addition, the levels of peripheral pro-inflammatory cytokines had no observable change in healthy controls after treatment by rTMS, which was consistent with the results of animal studies[15].

Nuclear factor-E2-related factor 2 (Nrf2) is a transcription factor that binds to antioxidant response elements and has anti-inflammatory effects in addition to anti-oxidative stress[16-18]. There was significantly reduced expression of Nrf2 both in the hippocampus and prefrontal cortex (PFC) of depressive-like mice induced by chronic social defeat stress or stress susceptible rats induced by learned helplessness[18,19]. Moreover, autopsy revealed that Nrf2 expression was decreased in the PFC region of MDD patients[19,20]. Tian *et al*[21] found that depressive-like behavior induced by chronic unpredictable mild stress (CUMS) in rats were improved by rTMS (15 Hz/1.26 T) *via* increasing Nrf2 translocation into the nucleus and decreasing the expression of TNFα, inducible nitric oxide synthase, IL-1β, and IL-6 in the hippocampus. When the *Nrf2*

Table 1 Main preclinical findings on antidepressant mechanisms of repetitive transcranial magnetic stimulation

Ref.	Model	rTMS				Main findings
		Frequency (Hz)	Intensity (T)	Duration (d)	Coil size	
Tian *et al*[21], 2020	CUMS	15	1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Regulation of Nrf2-induced anti-inflammatory effect in the hippocampus
Yang *et al*[42], 2019	CUS	1	20 mT	14	Not mentioned	Enhancement of synaptic plasticity in the hippocampus
Xue *et al*[45], 2019	CUS	5	1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Activation of the ECS in the hippocampus
Zhao *et al*[49], 2018	CUMS	10	50% of the resting motor threshold	15	5 cm in diameter (SD rats)	Decreasing the activity of the HPA axis
Heath *et al*[48], 2018	OB	10	50 mT	20	8 mm in diameter (C57BL/6J mice)	Activation of the BDNF signaling pathway and pro-proliferative in the hippocampus
Fang *et al*[43], 2018	CUMS	15	rTMS device maximum power	7	Not mentioned	Activation of the ECS in the hippocampus
Peng *et al*[68], 2017	CUS	5/10	0.84/1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Suppression of Sirt1/MAO-A signaling in the PFC
Chen *et al*[47], 2015	CUS	15	1.26	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Activation of the BDNF signaling pathway and pro-proliferative in the hippocampus
Wang *et al*[44], 2014	CUMS	15	rTMS device maximum power	7	Inner diameter 2.5 cm; outer diameter 5 cm (SD rats)	Activation of the ECS and BDNF signaling pathway in the hippocampus
Kim *et al*[78], 2014	CUMS	10	1.4	14	7 cm in diameter (SD rats)	Changing metabolic patterns in the brain
Feng *et al*[46], 2012	CUMS	15	rTMS device maximum power	21	Inner diameter 5 cm; outer diameter 7 cm (SD rats)	Decreasing the activity of the HPA axis, and activation of BDNF signaling pathway in the hippocampus
Tasset *et al*[29], 2010	OB	60	0.7 mT	14	Not mentioned	Anti-oxidative stress effects

BDNF: Brain derived neurotrophic factor; CUS: Chronic unpredictable stress; CUMS: Chronic unpredictable mild stress; ECS: Endocannabinoid system; HPA axis: Hypothalamic-pituitary-adrenocortical axis; MAO-A: Monoamine oxidase A; Nrf2: Nuclear factor-E2-related factor 2; OB: Olfactory bulbectomy; PFC: Prefrontal cortex; rTMS: Repetitive transcranial magnetic stimulation; SD rats: Sprague Dawley rats; Sirt1: Sirtuin 1.

gene was silenced, the anti-depressant effect of rTMS disappeared simultaneously with a decrease of inflammatory factors. The results suggested that rTMS plays an anti-depressant role *via* enhancement of an anti-inflammatory action mediated by the Nrf2 signaling pathway. However, the mechanism by which rTMS exerts its anti-depressant effect through an anti-inflammatory effect has not been fully elucidated. Therefore, more preclinical studies are needed in this respect.

ANTI-OXIDATIVE STRESS EFFECTS

Humans produce reactive oxygen species (ROS) in the process of using O_2 to oxidize glucose to generate adenosine triphosphate. Excessive ROS act on lipids, proteins, and deoxyribonucleic acid, and produce a large number of peroxidation products such as lipid peroxidation products malondialdehyde and 4-hydroxyalkenals, resulting in oxidative stress, which is considered an important factor for disease development. There are two types of anti-oxidative stress systems in the body: One is the enzymatic anti-oxidative stress system including glutathione peroxidase (GSH-Px) and superoxide dismutase; The other is the non-enzymatic anti-oxidative stress system including glutathione (GSH). Several meta-studies have shown increased peroxidation products and decreased anti-oxidative stress agents in MDD patients[22-25]. Durmaz *et al*[26] found that, compared with the value before treatment, the serum content of

thiol, an anti-oxidant organic sulfur, was reduced in TRD patients after treatment with 20 Hz (intensity, 110 % motor threshold) rTMS. However, there are different views on the anti-depressant effect of rTMS through anti-oxidative stress. Aydın *et al*[27] found that there was no difference in serum thioredoxin, a protein with anti-oxidant function, between healthy and TRD patients, or between TRD patients before and after rTMS treatment.

The review of Medina-Fernández *et al*[28] detailed the anti-oxidative stress effects of rTMS in a variety of diseases. In preclinical studies of depression, the mechanism of anti-oxidative stress in rTMS has been poorly studied. Compared with sham rTMS group, rTMS at 60 Hz/0.7 mT increased the decreased contents of GSH, GSH-Px, and superoxide dismutase, and decreased the contents of malondialdehyde, 4-hydroxyalkenals, and caspase-3, a key terminal shear enzyme in apoptosis, in brain tissue homogenate in a rat depression model induced by olfactory bulbectomy[29]. The idea that oxidative stress is one of the causes or characteristics of MDD has not been widely accepted by the academic community. In addition, the anti-depressive role of rTMS through the mechanism of anti-oxidative stress has been controversial in clinical studies, in which the measurement of oxidative stress markers in peripheral blood may not reflect the real situation in the brain truthfully and completely. Unfortunately, only one preclinical study was found to clarify the mechanism of anti-oxidative stress in the anti-depressive effect of rTMS.

ACTIVATION OF ENDOCANNABINOID SYSTEM AND BRAIN DERIVED NEUROTROPHIC FACTOR SIGNALING PATHWAY ENHANCES SYNAPTIC PLASTICITY AND NEUROGENESIS

Cumulative evidence suggests that the endocannabinoid system (ECS) is involved in the physiopathologic mechanism of depression[30-32]. ECS receptors include cannabinoid type 1 receptor (CB1R) and CB2R. ECS ligands include arachidonoyl ethanolamide (AEA), 2-arachidonyloglycerol (2-AG), noladine ether, virodhamine, and N-arachidonoyldopamine. Other endogenous compounds such as palmitoylethanolamide and oleylethanolamide also have affinity for the ECS receptors. AEA and 2-AG are the most important ligands in the ECS. The key proteins in AEA biosynthesis and decomposition are N-acyl phosphatidyl ethanolamine-phospholipase D and fatty acid amide hydrolase, respectively. The key proteins in 2-AG biosynthesis and decomposition are diacylglycerol lipase α (DAGLα) and monoacylglycerol lipase (MAGL), respectively. Endocannabinoids produced in the postsynaptic element activate endocannabinoid receptors located in the presynaptic membrane and perform a number of anti-depressant biological functions including: (1) Reducing the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis; (2) Enhancing hippocampal synaptic plasticity; (3) Promoting the neurogenesis of the hippocampus; and (4) Increasing the expression of brain derived neurotrophic factor (BDNF) in hippocampal tissue[33-36]. BDNF, a key factor affecting multiple signaling pathways in the brain, binds to the receptor TrkB on the membrane and activates the Ras/MAPK, PI3K/Akt, PLCγ, and GTPase signaling pathways to promote neurogenesis and enhance synaptic plasticity[37-41].

One Hz/20 mT rTMS increased the expression of synaptic proteins PSD95 and NR2B in the hippocampus of Wista rats with a depressive-like behavior induced by chronic unpredictable stress (CUS)[42]. rTMS at 15 Hz (intensity, device maximum power) reduced the expression of MAGL and Bax, increased the contents of 2-AG, CB1R, BDNF, and Bcl-2, and promoted neurogenesis in the hippocampus, improving depressive-like behavior induced by CUMS. CB1R antagonist (AM251) counteracts the biological function of the above mentioned rTMS[43,44]. rTMS at 5 Hz/1.26 T improved depressive-like behavior induced by CUS in rats *via* increasing the expression of CB1R, DAGLα, N-acyl phosphatidyl ethanolamine-phospholipase D, PSD95, and synaptophysin, and decreasing the expression of MAGL and fatty acid amide hydrolase in the hippocampus. The anti-depressant effect of rTMS was offset by short hairpin RNA targeting DAGL or CB1R[45]. The above preclinical studies suggested that rTMS plays an anti-depressant role by activating the ECS, which may provide evidence for the development of new anti-depressants targeting ECS.

Moreover, several preclinical studies have observed that rTMS increased the content of BDNF in the hippocampus and PFC, and promoted hippocampal neurogenesis in rodent CUMS, CUS, and olfactory bulbectomy depression models[44,46-49]. However, there are inconsistencies between the results of preclinical and clinical studies. BDNF

may be involved in hippocampal neurogenesis and synaptic plasticity as a neurotrophic factor, but the existence of a neuro-regenerative disorder hypothesis for depression is controversial. As compared with normal controls, the serum BDNF level markedly decreased in MDD patients, and significantly negatively correlated with the severity of depressive symptoms. In addition, in TRD patients carrying a homozygous BDNF Val/Val allele, the BDNF levels increased after treatment by rTMS[50,51]. However, the results of treatment effect were controversial in TRD patients, and it can be confirmed to be a predictor of treatment response in TRD patients. We included five relevant articles and conducted a mini meta-analysis using Review Manager 5.3 software[14,52-55]. It was found that serum BDNF levels in TRD patients increased after rTMS treatment (Figure 1A). Considering the issue of high heterogeneity, we applied the leave-one-out method to analyze the results[56], and found that after removing the study of Zhao *et al*[14], the heterogeneity decreased from 96% to 11%, and the conclusion that rTMS treatment had no effect on serum BDNF content in TRD patients was reached, which was consistent with the study results of Brunoni *et al*[57] (Figure 1B). BDNF is a macromolecular protein that does not easily cross the blood-brain barrier, which may be responsible for the inconsistency between the results of the above preclinical and clinical studies.

SUPPRESSION OF SIRTUIN 1/MONOAMINE OXIDASE A SIGNALING PATHWAY

Certain monoamine oxidase (MAO) inhibitors are used to treat patients with MDD, which include phenelzine, brofaromine, toloxatone, isocarboxazide, tranylcypromine, and moclobemide. MAO includes MAO-A and MAO-B subtypes in the brain, where MAO-A is involved in the metabolism of 5-hydroxytryptamine, norepinephrine, and dopamine, and MAO-B metabolizes dopamine, benzylamine, and phenethylamine[58-60]. Moreover, MAO-A produces ROS during the process of metabolizing monoamine neurotransmitters, which promotes neuronal apoptosis[61,62]. The expression of MAO-A is regulated by the transcription factors NHLH2, KLF11, R1, and FOXO1. Among them, NHLH2 and FOXO1 need to be deacetylated by Sirtuin 1 (Sirt1) to play the role of transcription factors[63-67]. Injection of Sirt1 inhibitor EX527 into the PFC of CUS rats improved depressive-like behavior. Further, the 5-hydroxytryptamine concentration in the PFC was increased by reducing the expression of Sirt1 and MAO-A and the activity of MAO, and the depressive-like behavior in CUS rats was improved after treatment by rTMS at 5 Hz/0.84 T, 5 Hz/1.26 T, 10 Hz/0.84 T, and 10 Hz/1.26 T[68]. MAO inhibitors take several weeks to demonstrate anti-depressant efficacy[69,70], whereas rTMS is not only effective in patients with TRD but also works faster than anti-depressants. Therefore, the Sirt1/MAO-A signaling pathway may not be a key mechanism for anti-depressant therapy in rTMS, especially for patients with TRD.

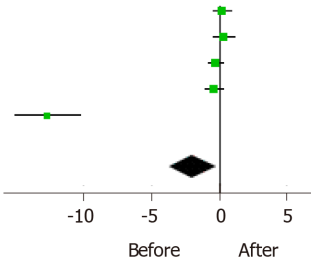
DECREASING THE ACTIVITY OF THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL AXIS

Hyperactivity of the HPA axis may be one of the pathophysiological mechanisms of depression[71-73]. Both preclinical and clinical studies have found increased activity of the HPA axis either in depressive-like animal models or in MDD patients. However, the results were contradictory, especially in clinical studies. There are many interfering factors for hormone levels, such as changes in circadian rhythm[74]. Drugs targeting the HPA axis have not been successful in clinical trials[70]. As a result, it has not been possible to use HPA related measurements in the diagnosis of MDD, and there may be many mechanisms that have not been clarified. rTMS at 10 Hz (intensity, 50 % of the resting motor threshold) and 15 Hz (intensity, device maximum power) reduced the levels of adrenocorticotropic hormone and cortisol in peripheral blood of depressive-like rats induced by CUMS[46,49]. There are few preclinical and clinical studies supporting that rTMS exerts an anti-depressant effect by reducing the activity of the HPA axis, and the current evidence is still insufficient.

A

Study or subgroup	Before mean	Before SD	Before Total	After mean	After SD	After Total	Weight	Std. mean difference IV, random, 95%CI
Gedge 2012	10.05	5.134	18	8.9	4.327	18	21.2%	0.24 [-0.42, 0.89]
Lang 2006	13.041	3.899	14	11.204	5.776	14	21.0%	0.36 [-0.39, 1.11]
Yukimasa 2006	2.53	2.01	26	3.11	2	26	21.4%	-0.28 [-0.83, 0.26]
Zanardini 2006	29.73	8.02	16	32.63	7.59	16	21.1%	-0.36 [-1.06, 0.34]
Zhao 2019	4.24	1.12	29	14.74	0.28	29	15.3%	-12.69 [-15.14, -10.24]
Total (95%CI)			103			103	100.0%	-1.95 [-3.69, -0.21]

Heterogeneity: Tau^2 = 3.62, Chi^2 = 104.09, df = 4 (P < 0.00001); I^2 = 96%
Test for overall effect: Z = 2.19 (P = 0.03)



B

Study or subgroup	Before mean	Before SD	Before Total	After mean	After SD	After Total	Weight	Std. mean difference IV, fixed, 95%CI
Gedge 2012	10.05	5.134	18	8.9	4.327	18	24.5%	0.24 [-0.42, 0.89]
Lang 2006	13.041	3.899	14	11.204	5.776	14	18.8%	0.36 [-0.39, 1.11]
Yukimasa 2006	2.53	2.01	26	3.11	2	26	35.2%	-0.28 [-0.83, 0.26]
Zanardini 2006	29.73	8.02	16	32.63	7.59	16	21.5%	-0.36 [-1.06, 0.34]
Total (95%CI)			74			74	100.0%	-0.05 [-0.38, 0.27]

Heterogeneity: Tau^2 = 3.37, df = 4 (P = 0.34); I^2 = 11%
Test for overall effect: Z = 0.32 (P = 0.75)

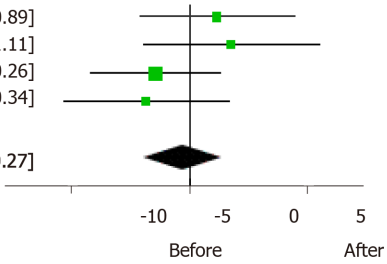


Figure 1 Forest plots of serum brain derived neurotrophic factor levels in treatment-resistant depression patients before and after repetitive transcranial magnetic stimulation treatment.

FUTURE PERSPECTIVES

This review summarizes several newly discovered anti-depressant mechanisms of rTMS in preclinical studies, including: (1) Anti-inflammatory effects mediated by activation of the Nrf2 signaling pathway; (2) Anti-oxidative stress effects; (3) Enhancement of synaptic plasticity and neurogenesis *via* activation of the ECS and BDNF signaling pathway; (4) Increasing the content of monoamine neurotransmitters *via* inhibition of the Sirt1/MAO-A signaling pathway; and (5) reducing the activity of the HPA axis.

Preclinical research has an incomparable huge advantage in obtaining brain specimens compared to clinical research. In the future preclinical research on rTMS mechanism, the following issues can be appropriately considered:

(1) The efficacy of rTMS is closely related to parameters, treatment time, and experimental protocol[75,76], and there is no unified treatment protocol in preclinical studies although it is available in clinical practice;

(2) Epidemiological studies show that the morbidity of females is higher than that of males for MDD[70,77]. However, all the studies in Table 1 used male rodents, which may be inappropriate or incomplete to elucidate the anti-depressant mechanisms of rTMS in animals;

(3) Different intensity of 10 Hz rTMS affects the metabolic patterns in the brain and periphery of the depression models[48,78]. rTMS at 1.4 T reduced the level of γ-amino butyric acid in the hippocampus and PFC regions of CUMS rats[78]. rTMS at 1 T increased the content of α-amino butyric acid and reduced the content of 3-methylhistidine in peripheral blood of mice suffering from olfactory bulbectomy[48]. Recently, proteomics and metabolomics techniques are gradually used to explore the anti-depressant mechanism of rTMS to focus on screening candidate biomolecule or biomarkers, which may provide a clue for further elucidating the relevant mechanisms;

(4) Preclinical studies have mostly focused on the hippocampus in animal models of depressive-like behavior. However, an increasing amount of evidence indicates that, other core brain regions are also closely associated with the development and progression of depression, such as the PFC, amygdala, cingulate gyrus, habenula, and

visual cortex[79-81], which should be considered in future studies. In addition, deep brain stimulation plays an important anti-depressant role in patients with MDD[82-85], suggesting that neural circuit dysfunction may be one of the mechanisms of depression[86]; however, there is no animal research to probe the regulation of neural circuits related to the anti-depressant effect of rTMS, which may be one of the future research directions;

(5) The shortcomings of TMS include inaccurate positioning and shallow depth of stimulation, which cause the difficulty to elucidate the neural circuit mechanism of up- and down-stream of the stimulation target region in animal models.

The left and right dorsolateral PFC of MDD patients have asymmetric low and high activity, respectively[87]. In clinical practice, high and/or low frequency rTMS are commonly used to stimulate the left and/or right side, respectively, to obtain anti-depressant effects. However, in preclinical studies, as shown in Table 1, due to the relatively large diameter of the coils of the rTMS device, it is not possible to accurately stimulate a specific brain region in rodents, and instead a large range of a hemisphere or even the whole brain is stimulated. This may be detrimental to the elucidation of the potential anti-depressant mechanism of rTMS. The development of rTMS devices for rats and mice with appropriate size and precise focus may be more conducive to exploring the mechanism of the anti-depressant effect of rTMS.

Another unavoidable defect of TMS is the problem of depth of stimulation, that is, TMS can only stimulate the superficial cerebral cortex, but has no stimulation effect on the subcortical brain regions[88]. Deep TMS can stimulate relatively deep brain regions compared to other TMS, but it may cause the superficial regions to be strongly stimulated[89]. In addition, TMS has energy consumption in non-target tissues such as the scalp, skull, and cerebrospinal fluid, which can reduce the energy occupancy rate of target tissues.

The application of a smaller size rTMS coil can achieve precise positioning, but the efficacy of the stimulation is insufficient and the therapeutic effect is affected. Exhilaratingly, enhancing the therapeutic effect by using magnetic nanoparticles may be in a creative way. Kong *et al*[90] found that magnetic nanoparticles could pass through the blood-brain barrier in mice. Furthermore, Li *et al*[91] intravenously injected magnetic nanoparticles with a core of Fe_3O_4 in rats, which can enhance the therapeutic effect of TMS. Our research team constructed a novel superparamagnetic Fe_2O_3 nanoparticle, accurately injected it into the left prelimbic cortex of CUMS mice treated by rTMS at10 Hz/0.1 T for 5 d, and significantly improving the depressive symptoms of these mice[92].

CONCLUSION

In conclusion, fully elucidating the anti-depressant mechanisms of rTMS will increase the chances of discovering new therapeutic strategies.

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ORIGINAL ARTICLE

Observational Study

Development of a depression in Parkinson's disease prediction model using machine learning

Haewon Byeon

ORCID number: Haewon Byeon 0000-0002-3363-390X.

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Haewon Byeon, Major in Medical Big Data, College of AI Convergence, Inje University, Gimhae 50834, Gyeonsangnamdo, South Korea

Corresponding author: Haewon Byeon, DSc, PhD, Professor, Major in Medical Big Data, College of AI Convergence, Inje University, Major in Medical Big Data, College of AI Convergence, Inje University, Gimhae 50834, Gyeonsangnamdo, South Korea. bhwpuma@naver.com

Abstract

BACKGROUND

It is important to diagnose depression in Parkinson's disease (DPD) as soon as possible and identify the predictors of depression to improve quality of life in Parkinson's disease (PD) patients.

AIM

To develop a model for predicting DPD based on the support vector machine, while considering sociodemographic factors, health habits, Parkinson's symptoms, sleep behavior disorders, and neuropsychiatric indicators as predictors and provide baseline data for identifying DPD.

METHODS

This study analyzed 223 of 335 patients who were 60 years or older with PD. Depression was measured using the 30 items of the Geriatric Depression Scale, and the explanatory variables included PD-related motor signs, rapid eye movement sleep behavior disorders, and neuropsychological tests. The support vector machine was used to develop a DPD prediction model.

RESULTS

When the effects of PD motor symptoms were compared using "functional weight", late motor complications (occurrence of levodopa-induced dyskinesia) were the most influential risk factors for Parkinson's symptoms.

CONCLUSION

It is necessary to develop customized screening tests that can detect DPD in the early stage and continuously monitor high-risk groups based on the factors related to DPD derived from this predictive model in order to maintain the emotional health of PD patients.

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Core Tip: When the effects of Parkinson's disease (PD) motor symptoms were compared using "functional weight", the occurrence of levodopa-induced dyskinesia was the most influential risk factor in the diagnosis of depression in Parkinson's disease (DPD). These results can be used as baseline information to prevent DPD and establish management strategies. It is necessary to develop customized screening tests that can detect DPD patients in the early stage and continuously monitor high-risk groups based on the factors related to DPD derived from this predictive model in order to maintain the emotional health of PD. It is also necessary to develop customized programs for managing depression from the onset of PD.

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INTRODUCTION

Parkinson's disease (PD) is a typical degenerative disease of the elderly with the second-highest incidence rate after Alzheimer's disease. The incidence rate of PD increases worldwide as the population ages. The Health Insurance Research and Assessment Service (2017)[1] reported that the number of patients with PD increased from 39265 in 2004 to 96499 in 2016, a 2.5-fold increase over 13 years, in South Korea. If the current trend in the aging population continues, the number of patients with PD will increase even further.

Although the primary symptom of PD is dyskinesia such as rigidity, it is highly likely that non-motor symptoms such as depression or cognitive impairment develop as PD progresses[2]. Among these symptoms, depressive symptoms are the most common non-motor symptoms of PD and previous studies[3-6] have reported that 35% to 75% of patients with PD suffer from depression, which is much higher than the prevalence of depression in adults in the local community (< 10%)[7]. Depression is known to adversely affect the quality of life in PD patients[8], and Parkinson's patients with depression have significantly higher anxiety symptoms, pessimism, suicidal thoughts, and self-condemnation compared to Parkinson's patients without depression[4,9]. Lee *et al*[10] analyzed 4362 patients with PD and reported that the elderly with PD had a 2-fold higher risk of suicide compared to healthy elderly. Even though patients with PD frequently experience depression[6,11], only 1% of them recognize that they have depression. These results suggest that it is necessary to diagnose depression in PD (DPD) as soon as possible[7,8]. Depression induced by PD requires social management and should not be considered a personal matter. As the symptoms of depression deteriorate as PD progresses, these symptoms, together with cognitive impairment, not only increase direct costs such as examinations and treatment but also raise indirect costs such as job loss due to disability and the care burden of supporting family members[12,13]. Ultimately, it causes unnecessary social expenditure at the national level. However, there are few studies on the characteristics and related factors of depression, a non-motor symptom of PD, compared to the motor symptoms of PD. Many medical practitioners are still more interested in the motor symptoms of PD than the non-motor symptoms. Moreover, depression is often misdiagnosed due to the non-motor and motor symptoms associated with PD[5]. It is important to diagnose depression in PD patients as soon as possible and identify predictors of depression to improve quality of life in PD patients.

It has been reported that the duration of PD, Hoehn and Yahr phase, age, activities of daily living, low cognitive function, and sleep behavior disorder affect DPD[5,14,15]. Depression frequently occurs during the early stages of PD[16]. Previous studies suspected that PD might cause depression along with dyskinesia due to dopamine

deficiency[6,17]. However, other studies showed that the administration of L-dopa (levodopa), a Parkinson's treatment, did not improve depression symptoms indisputably[18]. Therefore, it cannot be determined that depression is simply due to the effect of dopamine deficiency. On the other hand, many recent scholars have argued that depression in PD patients was caused by the complex interactions of multiple factors, rather than a single cause[19,20]. However, these previous studies[5,16,17] are limited in determining a risk factor, while considering multiple risk factors as each study used different confounding factors or covariates and used regression models to predict a risk factor, although they were effective in exploring individual risk factors. Additionally, regression analysis requires data which satisfy many assumptions such as normality, linearity, and homoscedasticity, and disease data are highly likely to violate these assumptions.

Recent studies have used various machine learning classifiers such as the support vector machine (SVM) and decision tree as statistical classification methods to identify multiple risk factors for diseases such as depression[21]. Of these, the SVM divides data into two groups linearly and explores the optimal boundary. SVM can be used for classifying nonlinear data, it has less probability of overfitting than the decision tree model, and it has high prediction accuracy even for small sample sizes[22,23]. The objectives of present study were to develop a model for predicting DPD based on the SVM, while considering sociodemographic factors, health habits, Parkinson's symptoms, sleep behavior disorders, and neuropsychiatric indicators as predictors and to provide baseline data for identifying DPD.

MATERIALS AND METHODS

Subjects

The present study was conducted by analyzing the Parkinson's Disease Epidemiology (PDE) Data provided by the National Biobank of Korea, the Centers for Disease Control and Prevention (CDC), and Republic of Korea (No. KBN-2019-005). This study was approved by the Research Ethics Review Board of the National Biobank of Korea (No. 2019-005) and the Korea-CDC (No. 2019-1327). The goal of the National Biobank and the structure of the data were described by Lee *et al*[24]. The PDE data used in this study were collected at 14 university hospitals from January to December, 2015, under the supervision of the Korea CDC. The PDE data consisted of health behaviors, sociodemographic factors, motor characteristics related to PD, disease history, neuropsychological test results and sleep behavior disorders. PD was diagnosed according to the idiopathic Parkinson's disease diagnosis criteria of the United Kingdom Parkinson's disease Society Brain Bank[25]. This study analyzed 223 of 335 patients who were 60 years or older with PD, after excluding 112 subjects who had a least one missing value in the Geriatric Depression Scale (GDS)[26], a depression screening test.

Measurement

Depression was measured using the 30 items of the GDS[26], and the threshold point of depression was 10 points. Explanatory variables included PD-related motor signs (*e.g.*, late motor complications, bradykinesia, tremor, postural instability, and rigidity), rapid eye movement (REM) and sleep behavior disorders, the Korean Mini Mental State Examination score[27], Korean Montreal Cognitive Assessment score[28], global Clinical Dementia Rating score (CDR)[29], Korean Instrumental Activities of Daily Living score (K-IADL)[30], Untitled Parkinson`s Disease Rating total score (UPDRS)[31], UPDRS motor score[32], Hoehn and Yahr staging (H and Y staging)[33], and the Schwab and England Activities of Daily Living scale (Schwab and England ADL)[34].

SVM was used to develop a DPD prediction model. SVM is a MLalgorithm that finds an optimal decision boundary, in other words, a linear separation dividing the hyperplane (H-plane) optimally, by converting training data to a higher dimension through nonlinear mapping[35]. For example, A = [b, e] and B = [c, f] are non-linearly (non-lin) separable in two dimensions. When they are mapped in three dimensions, they have linearly separable characteristics. Therefore, when appropriate non-lin mapping is conducted at sufficiently large dimensions, data with two classes can always be separated in H-plane[23].

SVM is very accurate as it can model complex nonlinear decision-making domains and tends to be overfitting less than other models, which is a major advantage of this method[36]. This study used R version 3.6.1 for statistical analyses. The prediction performance (accuracy) of eight SVM models was compared using four algorithms [

i.e., a radial basis function (Gauss function), a linear algorithm, a sigmoid algorithm, and a polynomial algorithm] and two types of SVM [C-SVM (C parameter) and Nu-SVM (Nu parameter)]. The prediction performance of the models was evaluated by considering overall accuracy, sensitivity, and specificity.

RESULTS

General characteristics of the 223 study subjects with PD were analyzed and are shown in Table 1. The mean age of the subjects was 71.7 years (SD = 6.1). The initial age at diagnosis of PD was 70.8 years (SD = 6.3) and the training period was 7.5 years (SD = 5.3). The percentage of non-smokers was 79.7%, right-handed subjects was 96.0%), and subjects without a family history of PD was 82.5%. It was found that 22.5% of the subjects had diabetes, 41.3% had hypertension, and 13.3% had hyperlipidemia. In terms of cognitive characteristics, 30.9% of the subjects had PDD, 61% had Mild Cognitive Impairment in Parkinson's disease (PD-MCI), and 8.1% of them had Parkinson's disease with cognitive impairment (PD-NC). The results of the GDS confirmed that 41.7% of the patients had depression. The distribution of neuropsychological test results is presented using a density plot (Figure 1).

Table 1 shows the general characteristics of the study subjects with depression and the related potential factors (influencing factors) of DPD. The results of the chi-square test showed that PD patients with depression and PD patients without depression were significantly different as assessed by the Korean Mini Mental State Examination, Korean Montreal Cognitive Assessment, Global CDR score, total score of UPDRS, sum of boxes in CDR, K-IADL, motor score of UPDRS, H and Y staging, and Chwab and England ADL ($P < 0.05$).

Comparing the accuracy of the DPD prediction model according to the SVM classification algorithm

The fit of the model varies by the kernel type of SVM. Therefore, our study compared the prediction accuracy of eight SVM models [(C-SVM or Nu-SVM) × (Gaussian kernel, linear, polynomial, or sigmoid algorithm)] to examine the performance of the models according to various kernel types (Table 2). The results of model fitting showed that the Gaussian Kernel-based Nu-SVM had the highest sensitivity (96.0%), specificity (93.3%), and mean overall accuracy (95%). On the other hand, although the polynomial-based C-SVM had the highest sensitivity (100%), it had the lowest specificity (20%) and the lowest mean overall accuracy (70%).

This study determined that the Gaussian algorithm-based Nu-SVM model, which had the highest sensitivity and overall accuracy, was the optimal model for predicting DPD and analyzed the importance of variables. The Gaussian algorithm-based Nu-SVM model utilized 34 support vectors and the "functional weight (importance of variables)" is presented in Table 3. Even though the functional weight of SVM is not a value simply for comparing the magnitudes of variables' influence or ranking the importance of variables, it is possible to compare the influence within the level of factors (*e.g.*, comparing the influence of gender) using it. It is also possible to understand whether the relationship between predictors and outcome variables is a risk factor or a preventive factor. The DPD prediction model revealed that the global CDR score, the sum of boxes in CDR, K-IADL, total UPDRS, motor UPDRS, age (≥ 75 years old), gender (female), education level (high school graduate or above), PD family history, smoking (21-40 packs per year), exposure to pesticides, postural instability, late motor complications (occurrence of levodopa-induced dyskinesia), late motor complications ("levodopa-induced dyskinesia" and occurrence of "wearing OFF"), and REM sleep behavior disorders were risk factors for depression. When the effects of PD motor symptoms were compared using "functional weight", late motor complications (occurrence of levodopa-induced dyskinesia) were the most influential risk factors for DPD.

DISCUSSION

Our study developed a depression prediction model using SVM for PD patients. This study used the hospital registry data and found that 41.7% of PD patients suffered from depression. Although it is difficult to compare directly, the results of this study were similar to the results of previous studies[4-6], showing that one in two PD patients

Table 1 General characteristics of the subjects with depression, *n* (%)

Characteristics	Depression		*P* value
	No (*n* = 130)	Yes (*n* = 93)	
Age			0.918
60-74 yr	83 (58.0)	60 (42.0)	
≥ 75 yr	47 (58.8)	33 (41.3)	
Sex			0.183
Male	62 (63.3)	36 (36.7)	
Female	68 (54.4)	57 (45.6)	
Education level			0.158
Middle school graduate and below	76 (54.7)	63 (45.3)	
High school graduate and above	54 (64.3)	30 (35.7)	
Handness			0.905
Right	125 (58.4)	89 (41.6)	
Left	2 (66.7)	1 (33.3)	
Both hands	2 (50.0)	2 (50.0)	
Family PD history			0.921
No	108 (58.7)	76 (41.3)	
Yes	9 (60.0)	6 (40.0)	
Pack year (smoking)			0.666
1-20 pack year	6 (42.9)	8 (57.1)	
21-40 pack year	5 (62.5)	3 (37.5)	
41-60 pack year	1 (50.0)	1 (50.0)	
61+ pack year	118 (59.3)	81 (40.7)	
Traumatic brain injury			0.852
No	118 (60.8)	76 (39.2)	
Yes	7 (63.6)	4 (36.4)	
Diabetes			0.214
No	103 (60.9)	66 (39.1)	
Yes	25 (51.0)	24 (49.0)	
Hypertension			0.246
No	71 (55.5)	57 (44.5)	
Yes	57 (63.3)	33 (36.7)	
Hyperlipidemia			0.220
No	114 (60.3)	75 (39.7)	
Yes	14 (48.3)	15 (51.7)	
Tremor			0.630
No	17 (54.8)	14 (45.2)	
Yes	107 (59.4)	73 (40.6)	
Rigidity			0.342
No	8 (72.7)	3 (27.3)	
Yes	120 (58.3)	86 (41.7)	
Bradykinesia			0.962

No	7 (58.3)	5 (41.7)	
Yes	121 (59.0)	84 (41.0)	
Postural instability			0.187
No	66 (64.1)	37 (35.9)	
Yes	59 (55.1)	48 (44.9)	
REM and RBD			0.081
No	58 (63.7)	33 (36.3)	
Yes	55 (51.4)	52 (48.6)	
Late motor complications			0.140
Only ON-OFF/Wearing OFF	12 (54.5)	10 (45.5)	
Only levodopa-induced dyskinesia	2 (22.2)	7 (77.8)	
Both ON-OFF/Wearing OFF and levodopa-induced dyskinesia are present	13 (59.1)	9 (40.9)	
Both ON-OFF / Wearing OFF and levodopa-induced dyskinesia are absent	99 (61.1)	63 (38.9)	
K-MMSE, mean ± SD	24.2 ± 4.6	21.5 ± 6.1	< 0.001
K-MoCA, mean ± SD	18.2 ± 6.1	13.9 ± 6.7	< 0.001
Global CDR score, mean ± SD	0.5 ± 0.3	0.8 ± 0.7	< 0.001
Sum of boxes in CDR, mean ± SD	2.3 ± 3.1	3.3 ± 4.0	0.041
K-IADL, mean ± SD	1.3 ± 3.0	3.2 ± 5.6	0.003
Total score of UPDRS, mean ± SD	34.5 ± 17.1	53.2 ± 26.1	< 0.001
Motor score of UPDRS, mean ± SD	22.7 ± 10.9	30.0 ± 13.5	< 0.001
H and Y staging, mean ± SD	2.2 ± 0.6	2.6 ± 0.9	0.002
Schwab and England ADL, mean ± SD	80.1 ± 14.5	67.3 ± 21.5	< 0.001

CDR: Clinical Dementia Rating; K-MMSE: Korean Mini-Mental State Examination; K-MoCA: Korean-Montreal Cognitive Assessment; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Untitled Parkinson`s Disease Rating total score; H and Y: Hoehn and Yahr; ADL: Activities of Daily Living.

Table 2 Comparing the accuracy of depression in Parkinson's disease prediction model, %

Type of algorithm	Overall accuracy	Sensitivity	Specificity
C-SVM: Linear	92.5	92.0	93.3
C-SVM: Polynomial	70.0	100	20.0
C-SVM: Gaussian	87.5	96.0	73.3
C-SVM: Sigmoid	85.0	88.0	80.0
Nu-SVM: Linear	90.0	92.0	86.6
Nu-SVM: Polynomial	92.5	92.0	93.3
Nu-SVM: Gaussian	95.0	96.0	93.3
Nu-SVM: Sigmoid	82.5	92.0	66.6

SVM: Support vector machine.

had depression. Despite the frequent occurrence of depression among patients with PD, the Global Parkinson's Disease Survey Steering Committee (2002)[8] reported that only 1% of patients with PD recognized that they had depression. These results imply that, even though PD patients frequently experience depression, it is highly likely that many PD patients, their caregivers, and their medical practitioners do not find

Table 3 Functional weight (importance of variables)

Variables	Functional weight
K-MMSE	-1.454
K-MoCA	-4.499
CDR (Global CDR score)	2.643
CDR (sum of boxes)	2.607
K-IADL	4.919
Total UPDRS	5.302
Motor UPDRS	0.978
H and Y staging	-2.190
Schwab and England ADL	-5.055
Age (60-74)	-3.638
Age (75+)	3.638
Gender (female)	0.345
Education (high school graduate and above)	1.150
Family PD history (yes)	0.232
Pack year (21-40)	0.032
Pack year (41-60)	0.000
Pack year (61+)	-1.032
Coffee (yes)	1.006
Pesticide exposure (currently not exposed but exposed previously)	-1.000
Pesticide exposure (currently exposed to pesticide)	2.264
Tremor (yes)	0.000
Rigidity (yes)	-1.000
Bradykinesia (yes)	0.675
Postural instability (yes)	1.117
LMC (levodopa-induced dyskinesia)	3.000
LMC (Both Wearing OFF and levodopa-induced dyskinesia are present)	0.264
LMC (Both Wearing OFF and levodopa-induced dyskinesia are absent)	-4.715
REM sleep behavior disorders	1.261
Number of support vectors: 34	

CDR: Clinical Dementia Rating; K-MMSE: Korean Mini-Mental State Examination; K-MoCA: Korean-Montreal Cognitive Assessment; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Untitled Parkinson`s Disease Rating total score; H and Y: Hoehn and Yahr; ADL: Activities of Daily Living; REM: Rapid eye movement; PD: Parkinson's disease.

depression symptoms in the patients or treat them as symptoms due to aging, and, consequently, the patients do not receive appropriate evaluation or treatment. Therefore, it is necessary to develop an education program in order to manage depression from the onset of PD so that PD patients and their caregivers can receive the correct information regarding depression and receive effective treatments. The results of this study showed that the global CDR score, the sum of boxes in CDR, K-IADL, total UPDRS, motor UPDRS, age (≥ 75 years old), gender (female), education level (≥ high school graduate), PD family history, smoking (21-40 packs per year), exposure to pesticides, postural instability, late motor complications (occurrence of levodopa-induced dyskinesia), late motor complications (occurrence of "wearing OFF" and "levodopa-induced dyskinesia"), and REM sleep behavior disorders were the major predictors of DPD. A number of studies[5,14,15] exploring the risk factors for DPD reported that daily living ability, sleep behavior disorders, cognitive level, and Hoehn

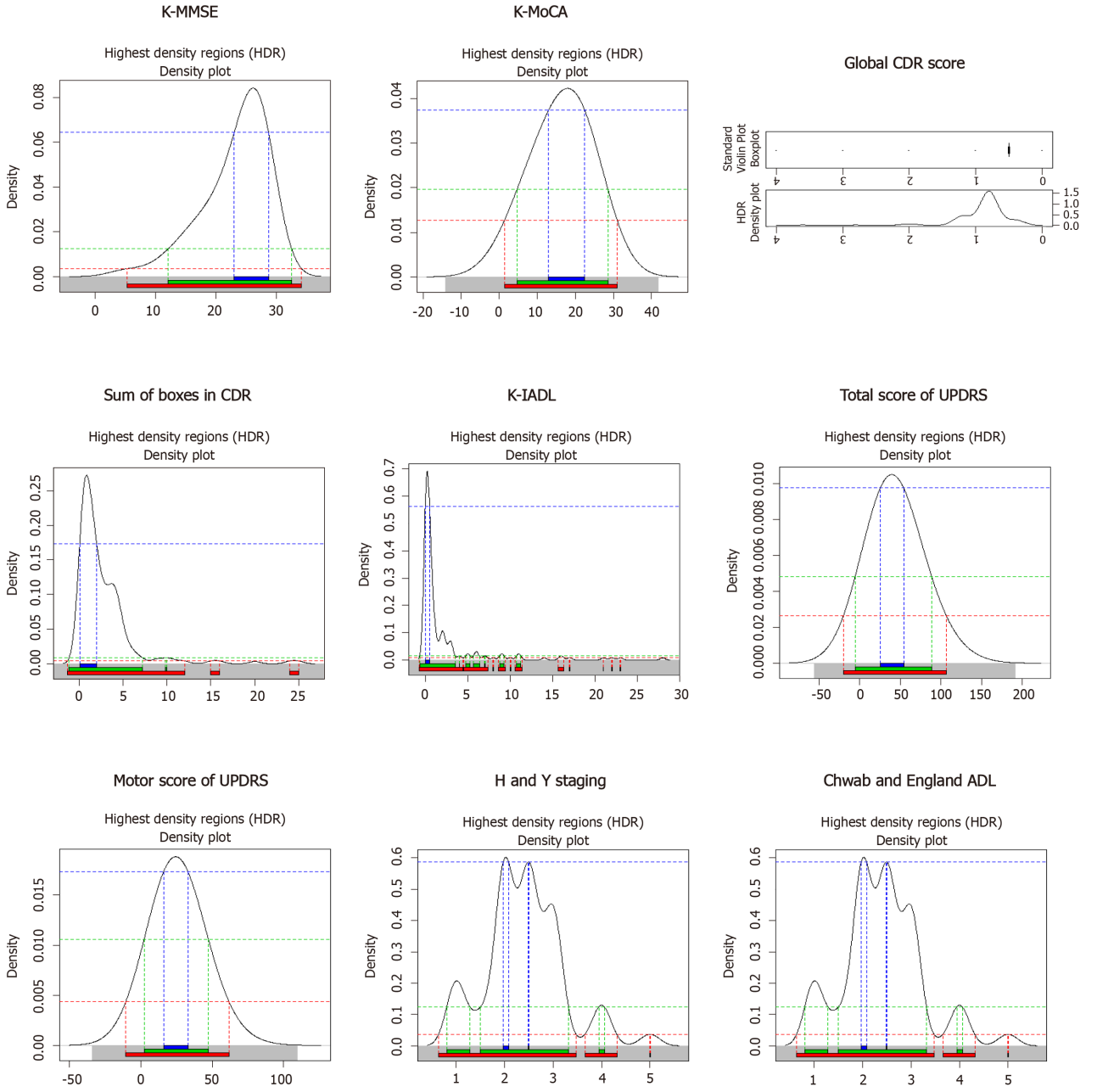


Figure 1 The distribution of neuropsychological tests. CDR: Clinical Dementia Rating; K-MMSE: Korean Mini-Mental State Examination; K-MoCA: Korean-Montreal Cognitive Assessment; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Untitled Parkinson`s Disease Rating total score; H and Y: Hoehn and Yahr; ADL: Activities of Daily Living.

and Yahr[33] stages, as well as environmental factors (*e.g.*, social stigma and social participation), were key influencing factors of depression and these results supported the results of our study. In particular, sleep behavior disorder is known to be the most representative factor for predicting the risk of depression[37] and has a high correlation with depression[38]. It is known that sleep behavior disorders are caused by dysfunction in the autonomic nervous system of patients with PD[39]. Bae *et al*[40] evaluated factors related to DPD using structural equation modeling, and reported that a sleeping issue best predicted DPD.

ADL, indicating the limitation of physical functions, is also related to early depression[41], as social relations can decrease due to limited ADL resulting in depression[42]. If depression persists, the quality of life in PD patients is highly likely to decrease[43] and they have a high risk of suicide[10]. Therefore, it is necessary to develop customized screening tools that can detect high-risk groups sensitively and conduct continuous monitoring in order to prevent depression and maintain emotional health.

Another finding of our study was that the prediction accuracy of the Gaussian kernel-based Nu-SVM was the highest when comparing eight SVM classification

algorithms [(C-SVM or Nu-SVM) × (Gaussian kernel, linear, polynomial, or sigmoid algorithm)]. The performance of non-lin SVM is affected by the kernel function and the parameters constituting it[44]. Of these, the Gaussian kernel is an algorithm that maps in a specific space with infinite dimension and it had high predictive accuracy in a previous study[25]. The results of this study suggest that, in the case of binary disease data with a small sample size, developing a prediction model using Gaussian kernel-based Nu-SVM will have higher predictive accuracy than SVM models based on other algorithms.

The present study was meaningful because it developed an SVM-based DPD prediction model using national Parkinson's registry data while considering sociodemographic factors, health habits, Parkinson's symptoms, and sleep behavior disorders as predictors in addition to neuropsychological indicators. The limitations of this study are as follows. First, it is difficult to generalize the results of this study as hospital registry data collected using convenience sampling was used. Future studies are needed to apply systematic sampling at the stage of recruiting subjects to minimize selection bias. Secondly, the sample size was small. Thirdly, causality could not be identified because it was a cross-sectional study. Additional longitudinal studies are required to prove causality. Fourthly, biomarkers and Parkinson's treatments related to depression were not investigated. In order to predict depression more sensitively, it is necessary to develop a predictive model including biomarkers in addition to cognitive tests and neuropsychological tests.

CONCLUSION

The results of our study can be used as baseline information to prevent DPD and establish management strategies. It is necessary to develop customized screening that can detect DPD in the early stage and continuously monitor high-risk groups based on the factors related to DPD derived from this predictive model in order to maintain the emotional health of PD patients. It is also necessary to develop customized programs for managing depression from the onset of PD.

ARTICLE HIGHLIGHTS

Research background

It is important to diagnose depression in Parkinson's disease (PD) patients as soon as possible and identify predictors of depression to improve the quality of life in PD patients.

Research motivation

It has been reported that the duration of PD, Hoehn and Yahr phase, age, activities of daily living, low cognitive function, and sleep behavior disorder affect depression in PD. However, these previous studies are limited in determining a risk factor, while considering multiple risk factors as each study used different confounding factors or covariates and used regression models to predict a risk factor, although they were effective in exploring individual risk factors.

Research objectives

The objectives of our study were to develop a model for predicting depression in Parkinson's disease (DPD) based on the support vector machine while considering sociodemographic factors, health habits, Parkinson's symptoms, sleep behavior disorders, and neuropsychiatric indicators as predictors and to provide baseline data for identifying DPD.

Research methods

The data used in this study was collected at 14 university hospitals from January to December, 2015, under the supervision of the Korea Centers for Disease Control. The data consisted of health behaviors, sociodemographic factors, motor characteristics related to PD, disease history, neuropsychological test results and sleep behavior disorders.

Research results

When the effects of PD motor symptoms were compared using "functional weight", late motor complications (occurrence of levodopa-induced dyskinesia) were the most influential risk factors for DPD.

Research conclusions

It is necessary to develop customized screening that can detect DPD in the early stage and continuously monitor high-risk groups based on the factors related to DPD derived from this predictive model in order to maintain the emotional health of PD patients.

Research perspectives

It is also necessary to develop customized programs for managing depression from the onset of PD.

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ABOUT COVER

Editorial board member of *World Journal of Psychiatry*, Dr. Lenin Pavón is an immunologist, having received his PhD at Instituto Politécnico Nacional (Mexico City, Mexico). Since 2000, he has served as Head of the Department of Psychoimmunology at Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñíz" in Mexico City. His career-long work has focused on studying the neuroendocrine-immune interactions in stress, major depression, fibromyalgia, schizophrenia, multiple sclerosis, and Alzheimer's disease. Dr. Pavón's research efforts have yielded a variety of professional awards as well as two books, 88 articles in indexed journals, and 19 chapters in specialized books. At present, he is a member of the editorial board of several international journals and scientific societies. His ongoing research interests involve inflammatory mediators' participation in psychiatric disorders and immunomodulation by neurotransmitters and hormones. (L-Editor: Filipodia)

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ORIGINAL ARTICLE

Case Control Study

Best early-onset Parkinson dementia predictor using ensemble learning among Parkinson's symptoms, rapid eye movement sleep disorder, and neuropsychological profile

Haewon Byeon

ORCID number: Haewon Byeon 0000-0002-3363-390X.

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Haewon Byeon, Department of Medical Big Data, College of AI Convergence, Inje University, Gimhae 50834, Gyeonsangnamdo, South Korea

Corresponding author: Haewon Byeon, DSc, PhD, Professor, Department of Medical Big Data, College of AI Convergence, Inje University, Gimhae 50834, Gyeonsangnamdo, South Korea. bhwpuma@naver.com

Abstract

BACKGROUND

Despite the frequent progression from Parkinson's disease (PD) to Parkinson's disease dementia (PDD), the basis to diagnose early-onset Parkinson dementia (EOPD) in the early stage is still insufficient.

AIM

To explore the prediction accuracy of sociodemographic factors, Parkinson's motor symptoms, Parkinson's non-motor symptoms, and rapid eye movement sleep disorder for diagnosing EOPD using PD multicenter registry data.

METHODS

This study analyzed 342 Parkinson patients (66 EOPD patients and 276 PD patients with normal cognition), younger than 65 years. An EOPD prediction model was developed using a random forest algorithm and the accuracy of the developed model was compared with the naive Bayesian model and discriminant analysis.

RESULTS

The overall accuracy of the random forest was 89.5%, and was higher than that of discriminant analysis (78.3%) and that of the naive Bayesian model (85.8%). In the random forest model, the Korean Mini Mental State Examination (K-MMSE) score, Korean Montreal Cognitive Assessment (K-MoCA), sum of boxes in Clinical Dementia Rating (CDR), global score of CDR, motor score of Untitled Parkinson's Disease Rating (UPDRS), and Korean Instrumental Activities of Daily Living (K-IADL) score were confirmed as the major variables with high weight for EOPD prediction. Among them, the K-MMSE score was the most important factor in the final model.

dataset available from the corresponding author at bhwpuma@naver.com.

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CONCLUSION

It was found that Parkinson-related motor symptoms (*e.g.*, motor score of UPDRS) and instrumental daily performance (*e.g.*, K-IADL score) in addition to cognitive screening indicators (*e.g.*, K-MMSE score and K-MoCA score) were predictors with high accuracy in EOPD prediction.

Key Words: Early-onset Parkinson dementia; Ensemble learning method; Neuropsychological test; Risk factor; Discriminant analysis; Naive Bayesian model

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Core Tip: It is believed that if the Korean Mini Mental State Examination (K-MMSE) is given priority over other cognitive screening tests in order to distinguish early-onset Parkinson dementia (EOPD) from Parkinson's disease, the accuracy of detecting EOPD will be higher than conducting other screening tests first. However, further epidemiological studies will be needed to fully comprehend the results of better accuracy of the K-MMSE than that of Korean Montreal Cognitive Assessment while detecting EOPD using the developed ensemble-based prediction model.

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INTRODUCTION

Dementia is a typical senile disease and indicates that a person with normal cognition experiences cognitive impairment due to various causes in the aging process. Dementia shows diverse symptoms, such as memory impairment; decreased cognitive functions, including language ability and frontal lobe executive function; and psychological symptoms of dementia (BPDS), depending on the type and progression of the disease[1]. It burdens caregivers psychologically and economically as well as the dementia patients[2]. In particular, care costs are extremely high as there is currently no cure for dementia, and it is necessary to take care of patients for a long time. As of 2019, South Korea spends KRW 14.6 trillion managing dementia, which is 0.8% of the GDP, and it is expected to increase more than seven times (KRW 106.5 trillion)[3]. It was reported that South Korea had 700000 dementia patients out of 7 million elderly people in 2017, which is already over 10% of the total elderly population[3]. It is approximately a 35% increase from 540000 dementia patients in 2012[3]. It tends to increase steadily by more than 7% per year[3]. Therefore, the reduction of dementia prevalence through the prevention, early diagnosis, and early management of dementia is the key to the mental health policy that the South Korean government must resolve as South Korea has an aging society.

Geriatricians evaluate the characteristics of dementia by classifying it into several types to diagnose dementia as soon as possible. Recently, many studies[4,5] examined the characteristics of the disease after categorizing it into early-onset dementia (EOD: Occurring before 65 years old) and late-onset dementia (LOD: Occurring at 65 years old or later) based on the onset of dementia symptoms (age). These studies revealed that EOD and LOD showed differences in imaging tests as the disease progressed. For example, in the case of Alzheimer's disease, EOD caused a greater loss of cerebral synapses or severe infiltration of senile plaques and neurofibrillary tangles than LOD[6-8]. Moreover, even the frontal and parietal lobes, as well as the temporal lobe, atrophied[6-8]. Additionally, since EOD patients are more likely to have a family history of dementia than LOD patients, it is suspected that EOD is affected by genetic predisposition more than LOD[7]. However, these imaging tests are not the ideal way to identify the onset of dementia in the early stages because they can only be used to diagnose dementia accurately by skilled medical personnel after dementia has progressed to some extent. Moreover, previous studies[9] that examined the

characteristics of EOD mostly evaluated Alzheimer's dementia. The demographic and neuropsychological characteristics of early-onset Parkinson dementia (EOPD) are relatively unknown.

In summary, despite the frequent progression from Parkinson's disease (PD) to Parkinson dementia (PDD), the basis to diagnose EOPD in the early stages is still insufficient. Currently, it is impossible to detect EOPD in the early stages just by using the cognitive screening test that is simply and commonly conducted for all types of dementia patients in South Korean public health centers. Although several biomarker candidates have been suggested based on the cerebrospinal fluid (CSF) test (*e.g.*, Aβ1-42 and total tau) for diagnosing dementia in the early stages[10], the CSF test is not versatile because it causes pain in examinees, thus examinees tend to reject the test, and the reliability of it cannot be tested; these are limitations of this test. In other words, because a range of factors (*e.g.*, gender, education level, and depression) affect EOPD[11-13], it would be necessary to develop a prediction model by applying PD motor and non-motor symptoms and sociodemographic indices[11,12] in addition to cognitive characteristics[14]. Byeon[15] argued that previous studies[16,17] were limited to the exploration of individual risk factors because they used regression models for predicting dementia and variables were quite limited because the prediction models mainly included neuropsychological tests. Therefore, there are limitations to developing a highly reliable model to predict EOPD using individual (single) indicators, such as PD symptoms and neuropsychological tests. In order to develop an accurate prediction model, it is necessary to develop a comprehensive model that includes sociodemographic indices, PD motor symptoms, PD non-motor symptoms, rapid eye movement (REM) sleep behavior disorder, and neuropsychological indices.

Recent studies have used machine learning algorithms as a method to predict a high disease risk group[18,19]. Machine learning is a process of analyzing relationships and rules in data to extract valuable information from the data. Random decision forest (RF) has been used widely; it produces many decision trees using an ensemble algorithm to overcome the limitations of overfitting and predicts target variables by combining them[20].

We are not aware of any published RF-based machine learning studies to analyze EOPD prediction capability by considering sociodemographic factors, PD motor symptoms, PD non-motor symptoms, REM sleep disorder, and neuropsychological profiles, together with cognitive function. This study explored the prediction accuracy of sociodemographic factors, PD motor symptoms, PD non-motor symptoms, and REM sleep disorder for diagnosing EOPD using a large-scale PD registry dataset.

MATERIALS AND METHODS

Participants

This study was performed by analyzing the Parkinson's Disease Epidemiology in Korea (PDEPI-Korea) multicenter registry data provided by the National Biobank of Korea (NB-Korea, No. KBN-2019-005). The study was approved by the Research Ethics Review Board of the NB-Korea (No. KBN-2019-005) and the Korea Centers for Disease Control and Prevention (Korea-CDC, No. KBN-2019-1327). The NB-K was founded in 2008 upon the approval of the Ministry of Health and Welfare due to the necessity of managing bio data systematically at the national level. It has been managed by the Korea CDC. The ultimate goal of the NBK is to promote biomedical research and public health. Please see Byeon[20] for details on the data source.

PD was diagnosed by a psychiatrist according to the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank[21]. In this study, PDD was defined as patients who met the diagnostic criteria of probable PDD, suggested by the Movement Disorder Society Task Force[22]. This study excluded patients who had other causative diseases, such as hydrocephalus and vascular Parkinsonism, determined from magnetic resonance imaging. This study analyzed 342 PD patients [66 EOPD patients and 276 PD patients with normal cognition (PD-NC)] who were younger than 65 years. Sample size calculations based on power analysis are shown in Figure 1. As the minimum number of samples calculated based on power analysis was 210 (group 1 = 105, group 2 = 105) with significance level (α) = 0.05, effect size d = 0.5 and power of test (1-β) = 0.95 on the standard of normal distribution, the number of samples (n = 342) in our study was appropriate.

Measurement

The outcome variable was defined as the presence of EOPD (yes or no), a binary

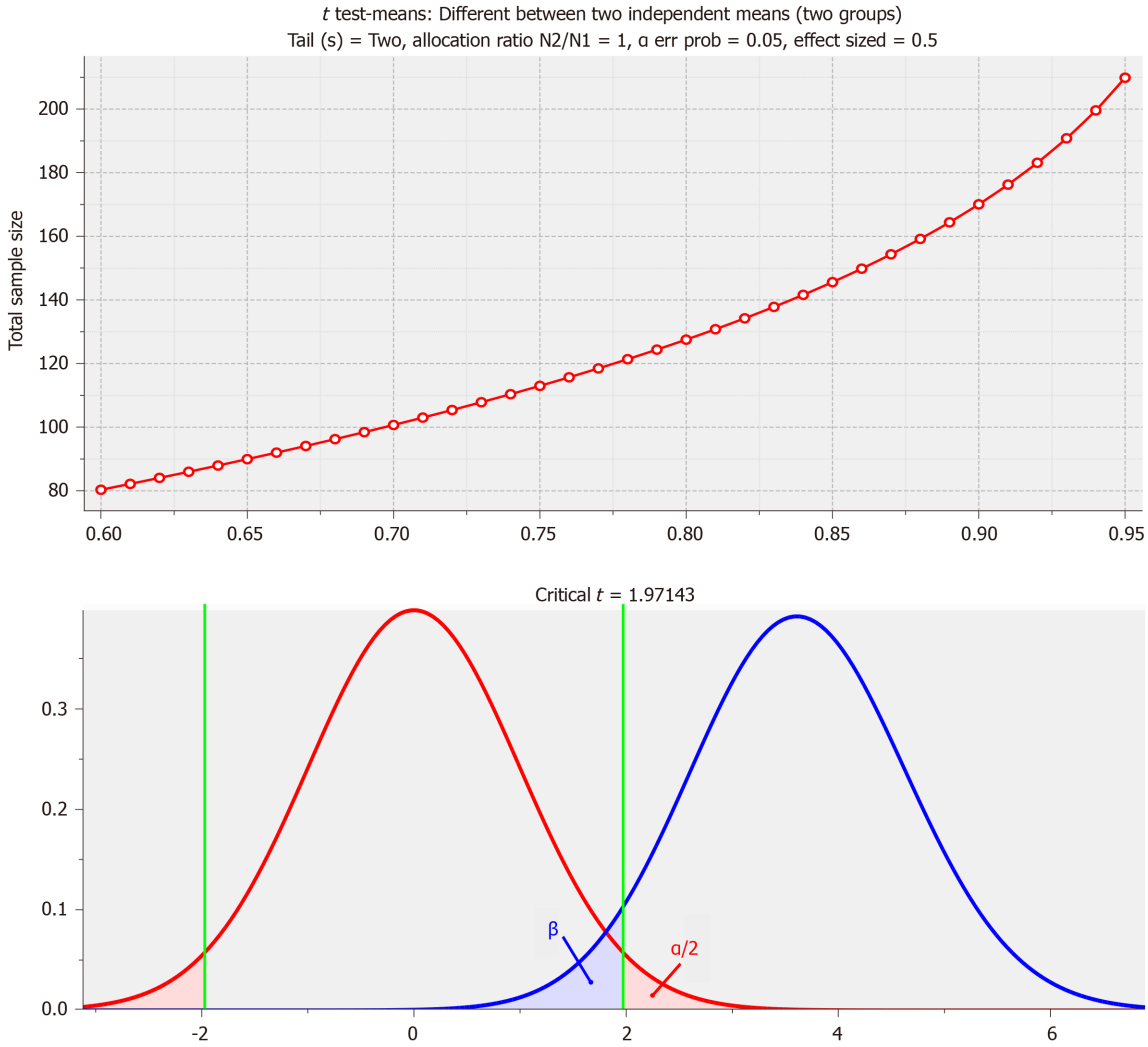


Figure 1 Sample size calculations.

variable, from a diagnosis by a neurologist. The explanatory variables included age; gender; education level (middle school graduate and below, or high school graduate and above); dominant hand (left hand or right hand); family PD history (yes or no); family dementia history (yes or no); pack-years (non-smoking, 1-20, 21-40, 41-60, or ≥ 61 pack-years); coffee-drinking (yes or no); coffee drinking period (no, ≤ 5, 6-9, or ≥ 10 years); mean coffee intake per day (no, ≤ 1, 2-3, or ≥ 4 cups); pesticide exposure recognition (never, currently not exposed but exposed previously, or currently exposed to pesticide); disease history (manganese poisoning, carbon monoxide poisoning, encephalitis, traumatic brain injury, stroke, alcoholism, diabetes, hyperlipidemia, hypertension, and/or atrial fibrillation); PD-related motor signs (tremor, akinesia/bradykinesia, postural instability, and/or late motor complications); neuropsychological characteristics determined by assessments such as the Korean Mini Mental State Examination (K-MMSE)[23], the Korean Montreal Cognitive Assessment (K-MoCA)[24], the sum of boxes in Clinical Dementia Rating (CDR)[25], the global CDR score[26], Korean Instrumental Activities of Daily Living (K-IADL)[27], the total score of Untitled Parkinson's Disease Rating (UPDRS)[28], the motor score of UPDRS[29], Hoehn and Yahr staging (H&Y staging)[30], and the Schwab & England Activities of Daily Living scale (Schwab & England ADL)[31]; and REM sleep behavior disorders. The definitions of the explanatory variables are shown in Table 1.

Development and evaluation of EOPD prediction model

The EOPD prediction model was developed using a RF algorithm and the accuracy of the developed model was compared with the naive Bayesian model and discriminant analysis. All analyses were performed using R version 3.5.2 (Foundation for Statistical Computing, Vienna, Austria).

RF is an ensemble classifier that randomly learns multiple decision trees and is a

Table 1 Measurement and definition of variables

Variable	Measurement	Characteristics
Sociodemographic factors	Age	Continuous variable
	Gender	Male or female
	Education	Middle school graduate and below or high school graduate and above
	Mainly used hand	Left hand, right hand, or both hands
	Family dementia history	Yes or No
	Family PD history	Yes or No
Environmental factors	Exposure to pesticide	Never, currently not exposed but exposed previously, or currently exposed to pesticide
Health behaviors	Pack-years	Non-smoking, 1-20, 21-40, 41-60, or ≥ 61 pack-years
	Coffee-drinking	Yes or No
	Mean coffee intake per day (cups/d)	No, ≤ 1, 2-3, or ≥ 4 cups
	Coffee drinking period (yr)	No, ≤ 5, 6-9, or ≥ 10
Disease history	Carbon monoxide poisoning	Yes or No
	Manganese poisoning	Yes or No
	Encephalitis	Yes or No
	Traumatic brain injury	Yes or No
	Stroke	Yes or No
	Alcoholism	Yes or No
	Diabetes	Yes or No
	Hypertension	Yes or No
	Hyperlipidemia	Yes or No
	Atrial fibrillation	Yes or No
Neuropsychological characteristics	Total score of KMMSE	Continuous variable
	Total score of KMoCA	
	Global CDR score	
	Sum of boxes in CDR	
	K-IADL	
	Total score of UPDRS	
	Motor score of UPDRS	
	H&Y staging	
	Schwab & England ADL	
Sleep behavior disorders	REM sleep behavior disorders	Yes or No
Exercise characteristics related to PD (PD related motor signs)	Tremor	Yes or No
	Rigidity	Yes or No
	Bradykinesia	Yes or No
	Postural instability	Yes or No
	LMC	Yes or No

PD: Parkinson's disease; KMMSE: Korean Mini Mental State Examination; KMoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Score of Untitled Parkinson's Disease Rating; H&Y staging: Hoehn and Yahr staging; Schwab & England ADL: Schwab & England Activities of Daily Living scale; REM: Rapid eye movement; LMC: Late motor complications.

machine learning method based on the meta-learning of decision trees. It consists of a training stage composing many decision trees and a test stage that classifies or predicts when an input vector is entered.

The ensemble form of training data can be expressed as Forest F = {f1,… , fn}. The distributions obtained from the decision trees of each forest were averaged by the number (T) of decision trees and were then classified. For combining the predictors of each sample, the average was used when the target variable was a continuous variable, and the majority vote was used when it was a categorical variable (Figure 2).

RF is similar to bagging in that it improves stability by combining decision trees generated from multiple bootstrap samples, based on the majority rule. However, it is conceptually different from bagging because it uses explanatory variables, which are randomly selected in each bootstrap sample. The RF can be theoretically free from overfitting because it contains randomness for both features and learning instances. Moreover, it is not much affected by noise or outliers and it is more accurate than other machine learning methods, such as decision trees. The accuracy of RF increases when the number of trees increases. However, it may suffer from an elbow point, indicating a steep decrease in slope. Moreover, each tree is more likely to have a more complex structure when non-critical explanatory variables are selected. Consequently, this study used the grid search method that can minimize problems such as elbow point by considering mtry number (n_estimator), indicating the number of candidates for explanatory variables among RF hyperparameters in advance. The procedure of developing an RF-based prediction model is presented in Figure 3.

Comparison of model prediction accuracy

This study selected an algorithm with the best model performance as the final model by comparing the overall accuracy of RF, discriminant analysis, and the naive Bayesian model. Moreover, this study showed the variable importance of the final model. A partial dependence plot was presented to visually confirm the marginal effects of an input variable with the highest importance on a response variable. The function of partial dependence is given in the following Equation.

In the above equation, $p_1(x, x_{ic})$ is Pr (Y = 1), calculated from a specific value of an interest variable (x) and a fixed value of the remaining predictor (x_{ic}). This probability is calculated as the ratio classified as Y = 1 category in the corresponding random decision tree. In other words, partial dependence and the log odds of the logic model share the same concept, and it is the mean after calculating the log odds from all observations *i*.

RESULTS

General characteristics of the participants

The general characteristics of 342 participants with PD were analyzed (Table 2). The mean age of the subjects was 57.3 years old (SD = 5.7). The initial age at diagnosis of PD was 56.7 years old (SD = 5.9). Smokers made up 88.6% of the participants, subjects with a family history of PD were 5.1% of the participants, and subjects with a family history of dementia were 7.4% of the participants. It was found that 19.3% of the subjects had EOPD.

Development of the EOPD prediction model using RF

This study changed mtry values, presenting the number of explanatory variables to be used in the decision tree constituting RF, from 3 to 13, and selected values with the smallest error of Out-Of-Bag. The changes in the error of Out-Of-Bag are presented in Table 3. The optimal mtry to be applied in this study was 4, showing the lowest error rate (10.5%). When n tree, the number of tree generations, and mtry were set as 500 and 4, respectively, the final RF model of this study had an overall accuracy of 89.5%.

Selection of the final EOPD prediction model

The overall accuracy of the RF was 89.5%, and it was higher than that of both discriminant analysis (78.3%) and the naive Bayesian model (85.8%). Therefore, the RF was assumed to be the most accurate prediction model among EOPD prediction models, and it was selected as the final prediction model. In Figure 3, the black line indicates the changes in each error rate against 500 bootstrap samples. Figure 4 shows that the changes in error rate became relatively stable when the number of bootstrap samples exceeded 60. Additionally, the multidimensional scaling plot of RF, which

Table 2 General characteristics of the subjects (*n* = 342)

Characteristics	*n* (%)
Age, mean ± SD (yr)	57.3 ± 5.7
K-MMSE, mean ± SD	25.6 ± 4.0
K-MoCA, mean ± SD	21.2 ± 5.1
Global CDR score, mean ± SD	0.4 ± 0.3
Sum of boxes in CDR, mean ± SD	1.5 ± 1.7
K-IADL, mean ± SD	1.0 ± 2.4
Total score of UPDRS, mean ± SD	41.3 ± 21.8
Motor score of UPDRS, mean ± SD	23.1 ± 11.1
H&Y staging, mean ± SD	2.3 ± 0.6
Schwab & England ADL, mean ± SD	77.5 ± 15.0
Gender	
Male	174 (50.9)
Female	168 (49.1)
Education	
Middle school graduate and below	195 (57.0)
High school graduate and above	147 (43.0)
Handness	
Right	318 (93.0)
Left	15 (4.4)
Both hands	9 (2.6)
Family PD history	
No	279 (94.9)
Yes	15 (5.1)
Family dementia history	
No	264 (92.6)
Yes	21 (7.4)
Smoking (pack year)	
1-20	18 (7.9)
21-40	9 (2.6)
41-60	3 (0.9)
61+	303 (88.6)
Coffee consumption	
No	174 (50.9)
Yes	168 (49.1)
Carbon monoxide poisoning	
No	294 (93.3)
Yes	21 (6.7)
Traumatic brain injury	
No	306 (97.1)
Yes	9 (2.9)
Diabetes	

No	276 (82.3)
Yes	60 (17.7)
Hypertension	
No	249 (73.5)
Yes	90 (26.5)
Hyperlipidemia	
No	303 (89.4)
Yes	36 (10.6)
Atrial fibrillation	
No	336 (99.1)
Yes	3 (0.9)
Tremor	
No	120 (36.0)
Yes	213 (64.0)
Rigidity	
No	24 (7.2)
Yes	309 (92.8)
Bradykinesia	
No	21 (6.3)
Yes	312 (93.7)
Postural instability	
No	159 (50.5)
Yes	156 (49.5)
REM sleep behavior disorders	
No	195 (61.3)
Yes	123 (38.7)
Late motor complications	
Only ON-OFF/Wearing OFF	57 (17.9)
Only levodopa-induced dyskinesia	12 (3.8)
Both ON-OFF/Wearing OFF and levodopa-induced dyskinesia are present	48 (15.1)
Both ON-OFF/Wearing OFF and levodopa-induced dyskinesia are absent	201 (63.2)
Depression	
No	147 (67.1)
Yes	72 (32.9)

K-MMSE: Korean Mini Mental State Examination; K-MoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Score of Untitled Parkinson's Disease Rating; H&Y staging: Hoehn and Yahr staging; Schwab & England ADL: Schwab & England Activities of Daily Living; PD: Parkinson's disease; REM: Rapid eye movement.

visualizes the classification results through a two-dimensional diagram, is presented in Figure 5.

Importance of variables in the final EOPD prediction model

The normalized importance of variables in the RF model, the final model, is presented in Figure 6 and Table 4. In this model, K-MMSE score, K-MoCA score, sum of boxes in CDR, global score of CDR, motor score of UPDRS, and K-IADL score were confirmed as the major variables with high weight for EOPD prediction. Among them, K-MMSE score was the most important factor in the final model.

Table 3 Error of Out-Of-Bag

Mtry (*n*)	Error of Out-Of-Bag
3	0.140
4	0.105
5	0.149
6	0.132
7	0.140
8	0.123
9	0.149
10	0.123
11	0.140
12	0.158
13	0.149

The partial dependence plot for K-MMSE, the most important variable in the EOPD prediction model, is presented in Figure 7. When the other factors (variables) were identical, the probability of the absence of EOPD tended to decrease as K-MMSE scores increased (Figure 6). In other words, it was confirmed that K-MMSE had the largest impact on EOPD prediction even after adjusting for other neuropsychological tests, PD symptoms, medical history, REM sleep disorder, depression, and sociodemographic factors.

DISCUSSION

Choosing a test with high feasibility and accuracy is critical to easily detect EOPD from PD in the point-of-care environment. It is required to comprehensively compare prediction accuracy for various predictors of EOPD, such as neuropsychological tests, lifestyle, sociodemographic factors, PD symptoms, depression, and REM sleep disorders. This study analyzed the prediction accuracy of various cognitive screening tests and neuropsychological profiles that could distinguish EOPD from PD using RF. The tests were ranked from greatest to least accurate as follows: K-MMSE score, K-MoCA score, sum of boxes in CDR, global score of CDR, motor score of UPDRS, and K-IADL score. It is noteworthy that the motor score of UPDRS, in addition to cognitive screening tests, was an important test in predicting EOPD. This is probably because participants with EOPD were more likely to show non-typical symptoms, such as movement problems, gait problems, and coordination problems[22], and the motor score of UPDRS could comprehensively measure these PD motor symptoms.

In this study, K-MMSE score was the most important neuropsychological test for detecting EOPD. Moreover, the accuracy of K-MMSE was higher than that of K-MoCA. An essential factor in the diagnosis of EOPD is a decline in cognitive function that began after the onset of PD. This decline in cognitive function gradually progresses in various domains, such as executive function, memory, and visuospatial function. In particular, it has been reported that PDD patients experience impaired executive functions, reflecting the decrease in the ability to solve problems from the early stages of dementia[32] as well as impaired visuospatial function[33]. It is known that the impairment of other types of dementia, such as Alzheimer's disease, was significantly lower than that[34]. K-MMSE and K-MoCA have been widely used as screening tests that simply compare the decline of various cognitive functions by types and comprehensively assess cognitive functions prior to in-depth tests in the point-of-care environment. The results of this study showed that the accuracy of K-MMSE was higher than that of K-MoCA when distinguishing EOPD from PD. Therefore, it is believed that if K-MMSE is given priority over other cognitive screening tests in order to distinguish EOPD from PD, the accuracy of detecting EOPD will be higher than conducting other screening tests first. However, further epidemiological studies will be needed to fully comprehend the results of the better accuracy of K-MMSE than that of K-MoCA while detecting EOPD, using the developed ensemble-based prediction

Table 4 The normalized importance of variables in the random forest model

Variables	Mean decrease Gini
K-MMSE	7.224
K-MoCA	2.992
Sum of boxes in CDR score	2.872
Global CDR score	2.304
Motor UPDRS	2.104
K-IADL	1.720
Total UPDRS	1.587
Schwab & England ADL	1.258
H&Y staging	1.040
Late motor complications	0.775
Consumption of coffee	0.699
Education level	0.527
Pack year	0.505
BDI	0.409
Tremor	0.338
Postural instability	0.338
Rigidity	0.331
Gender	0.255
REM sleep behavior disorders	0.249
Hypertension	0.168
Handness	0.151
Diabetes	0.146
Hyperlipidemia	0.129
Carbon monoxide poisoning	0.124
Family PD history	0.074
Family dementia history	0.066
Bradykinesia	0.034
Manganese poisoning	0.013
Traumatic brain injury	0.002
Atrial fibrillation	< 0.001

K-MMSE: Korean Mini Mental State Examination; K-MoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Score of Untitled Parkinson's Disease Rating; H&Y staging: Hoehn and Yahr staging; Schwab & England ADL: Schwab & England Activities of Daily Living; PD: Parkinson's disease; REM: Rapid eye movement; BDI: Beck Depression Inventory.

model. Machine learning has the disadvantage of being unable to interpret the derived results, although it has better prediction accuracy than the traditional regression model. Therefore, future studies are required to develop explainable artificial intelligence models that have high prediction accuracy and are able to interpret results.

Another finding of this study was that the accuracy of RF was higher than that of both the naive Bayesian model and discriminant analysis. These results agreed with Byeon[35], which showed that the ensemble algorithm was more accurate than a regression analysis or decision trees for predicting cognitive impairment in old age. RF has high prediction performance because it generates various decision trees from a number of bootstrap samples, and the possibility of overfitting is low[35]. In particular,

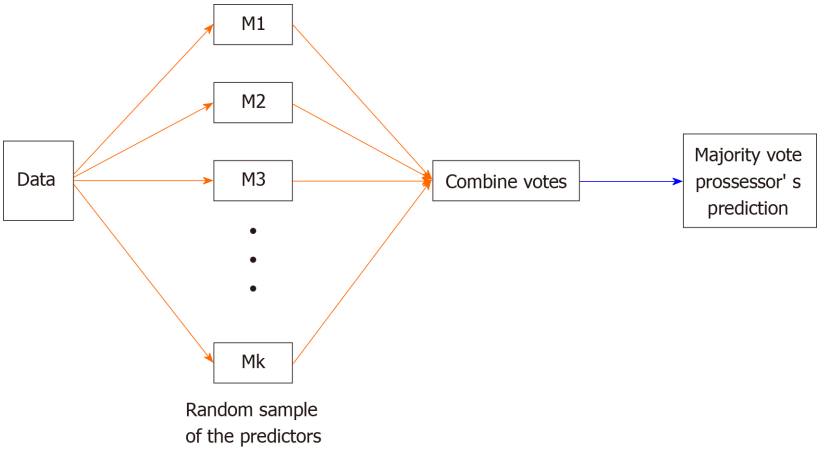


Figure 2 The random forest.

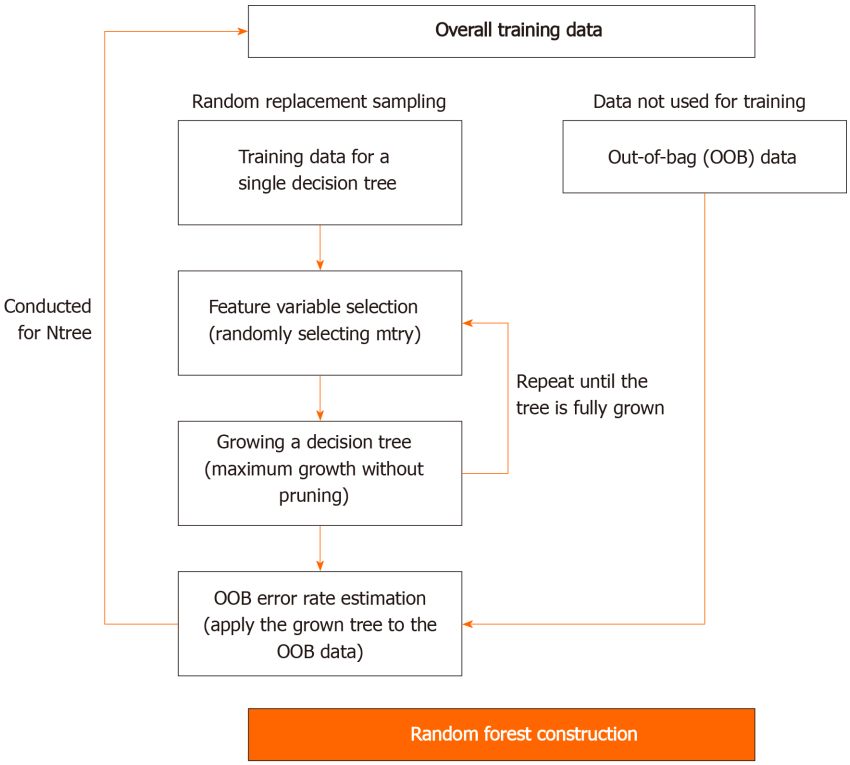


Figure 3 The development process of a random decision forest-based prediction model.

Equation: $f(x) = \frac{1}{n}\sum_{i=1}^{n} log\left(\frac{p_1(x, x_{ic})}{p_0(x, x_{ic})}\right)$

RF showed good predictive performance even when classifying binary variables using imbalanced disease data[15,18]. Therefore, it is believed that, compared to traditional statistical techniques such as discriminant analysis, using RF will increase accuracy while exploring major variables, allowing us to predict EOPD.

The importance of this study was that it identified the prediction accuracy of sociodemographic factors, PD motor symptoms, PD non-motor symptoms, REM sleep disorder, and neuropsychological profiles for distinguishing EOPD from PD, using national examination data conducted by the National Biobank of Korea. The limitations of the study are as follows: (1) The data source of this study was the registry data of multiple institutions and subjects were not randomly sampled; (2) The prediction model did not include candidate markers, genetic information, or biomarkers; (3) Genes such as *PRKN* and *LRRK2* are known to be risk factors for PD

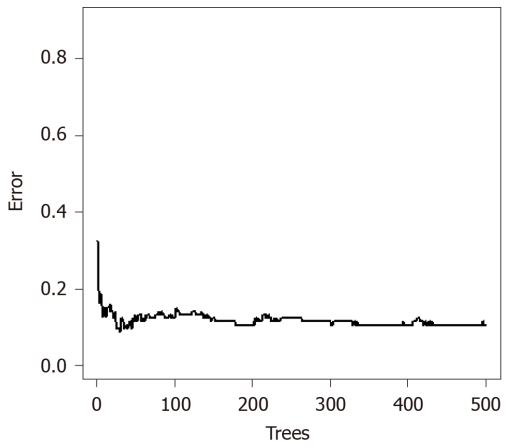


Figure 4 Error rate of the random forest model (500 trees).

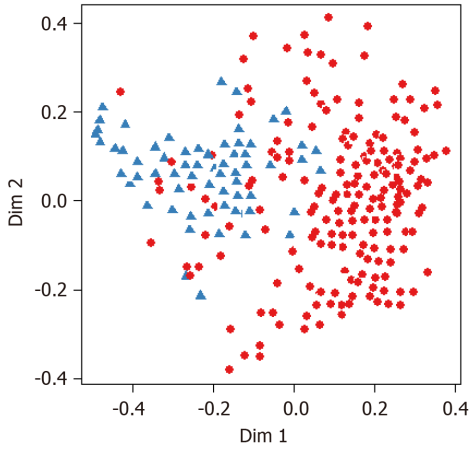


Figure 5 Multidimensional scaling plot of random forest (blue = early-onset Parkinson dementia and red = Parkinson's disease)

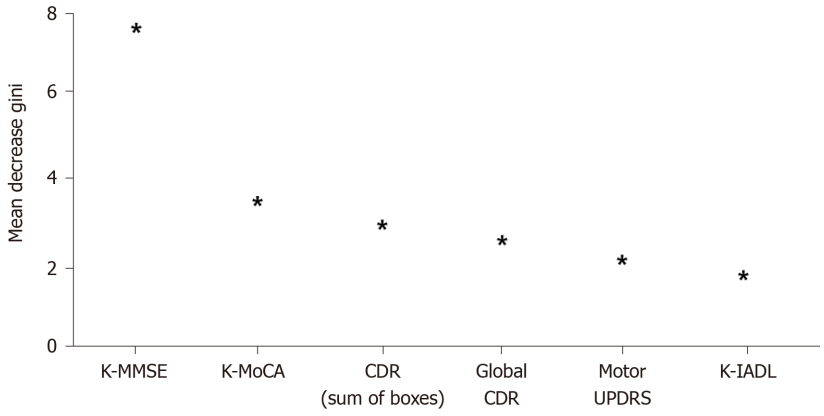


Figure 6 Importance of variables in the random forest-based early-onset Parkinson dementia prediction model (only the top six are presented). K-MMSE: Korean Mini Mental State Examination; K-MoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Score of Untitled Parkinson's Disease Rating.

and highly related to cognitive functions; and (4) Even though administration of PD medicine could affect the results of cognitive tests, it was not considered as an input variable of the prediction model. Therefore, it is expected that it will be possible to derive more clinically meaningful results when a prediction model is developed by including genetic information or biomarkers in addition to neuropsychological tests. Furthermore, since PD medicine influences the expression of behavioral symptoms

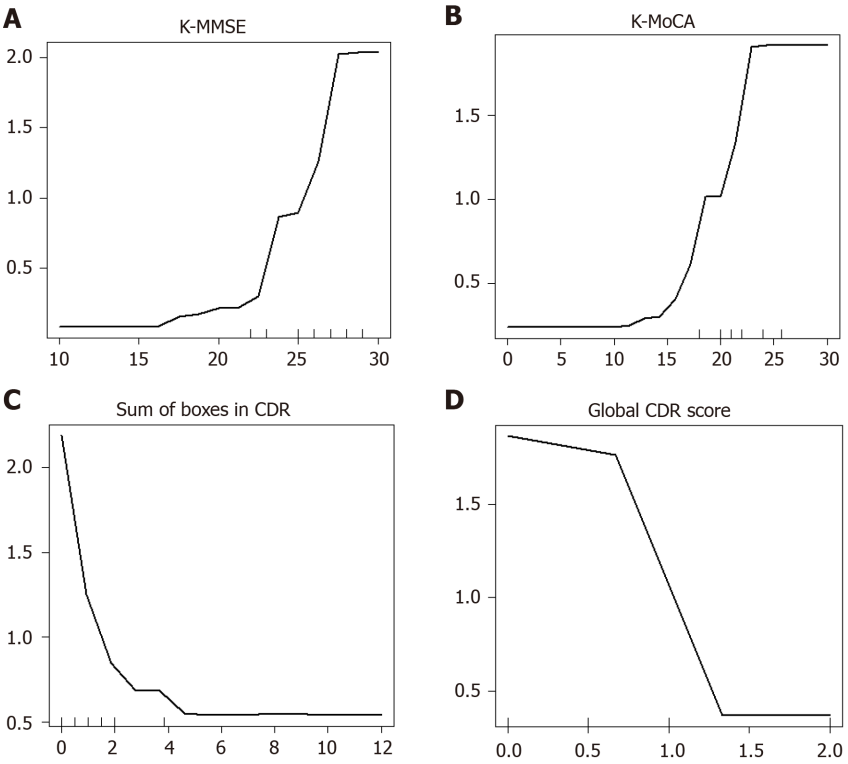


Figure 7 Partial dependence plot. K-MMSE: Korean Mini Mental State Examination; K-MoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating.

and cognitive symptoms, it is necessary to investigate the application of it when developing an EOPD prediction model in the future.

CONCLUSION

It was found that Parkinson-related motor symptoms (*e.g.*, motor score of UPDRS) and instrumental daily performance (*e.g.*, K-IADL score), in addition to cognitive screening indicators (*e.g.*, K-MMSE score and K-MoCA score), were highly accurate predictors in EOPD prediction. Moreover, the accuracy of RF was higher than that of both the naive Bayesian model and discriminant analysis. This study showed the need for a customized screening test that can detect EOPD early using biomarkers or genetic big data.

ARTICLE HIGHLIGHTS

Research background

Despite the frequent progression from Parkinson's disease (PD) to Parkinson dementia, the basis to diagnose early-onset Parkinson dementia (EOPD) in the early stage is still insufficient.

Research motivation

It is limited to develop a highly-reliable model to predict EOPD using individual indicators such as PD symptoms and neuropsychological tests. In order to develop an accurate prediction model, it is necessary to develop a comprehensive model that includes sociodemographic indices, Parkinson's motor symptoms, Parkinson's non-motor symptoms, rapid eye movement (REM) sleep behavior disorder, and neuropsychological indices.

Research objectives

The objectives of our study were to explore the prediction accuracy of sociodemographic factors, Parkinson's motor symptoms, Parkinson's non-motor

symptoms, and REM sleep disorder for diagnosing EOPD using PD multicenter registry data.

Research methods

This study was performed by analyzing the Parkinson's Disease Epidemiology multicenter registry data provided by the National Biobank of Korea. This study analyzed 342 Parkinson patients (66 EOPD patients and 276 PD patients with normal cognition, younger than 65 years). The EOPD prediction model was developed using a random forest algorithm and the accuracy of the developed model was compared with the naive Bayesian model and discriminant analysis.

Research results

When the factors of EOPD were compared using "normalized importance of variables", the Korean Mini Mental State Examination score was the most important factor of EOPD. Also, the accuracy of random decision forest was higher than that of naive Bayesian model and that of discriminant analysis.

Research conclusions

It is believed that using random forest will increase accuracy while exploring major variables allowing us to predict EOPD, compared to traditional statistical techniques such as discriminant analysis.

Research perspectives

It is necessary to develop a customized screening test that can early detect EOPD using biomarkers or genetic big data.

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ORIGINAL ARTICLE

Observational Study

Testing the hypothesis of subtypes of nonadherence in schizophrenia and schizoaffective disorder: A prospective study

Dulcinea Vega, Francisco J Acosta, Pedro Saavedra

ORCID number: Dulcinea Vega 0000-0002-7360-3967; Francisco J Acosta 0000-0001-5835-2795; Pedro Saavedra 0000-0003-1681-7165.

Author contributions: Acosta FJ designed the study and wrote the protocol, wrote the first draft of the manuscript, and coordinated the project; Vega D managed the literature searches and was in charge of the recruitment and assessments of all patients; Saavedra P was in charge of data management and undertook the statistical analysis; and all authors contributed to and have approved the final manuscript.

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Dulcinea Vega, Department of Psychiatry, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria 35016, Las Palmas, The Canary Islands, Spain

Dulcinea Vega, Francisco J Acosta, Department of Psychiatry, Insular University Hospital of Gran Canaria, Las Palmas de Gran Canaria 35016, Las Palmas, The Canary Islands, Spain

Francisco J Acosta, Department of Mental Health General Management of Healthcare Programs, Canary Islands Health Service, Las Palmas de Gran Canaria 35004, Las Palmas, The Canary Islands, Spain

Francisco J Acosta, Research Network on Health Services for Chronic Conditions (REDISSEC), Carlos III Health Institute, Madrid 28029, Spain

Pedro Saavedra, Department of Mathematics, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria 35016, Las Palmas, The Canary Islands, Spain

Corresponding author: Francisco J Acosta, MD, PhD, Doctor, Department of Mental Health General Management of Healthcare Programs, Canary Islands Health Service, Las Palmas de Gran Canaria 35004, Las Palmas, The Canary Islands, Spain. fjacostaartiles@hotmail.com

Abstract

BACKGROUND

Nonadherence is a major problem in the treatment of psychotic disorders. It has been hypothesized that nonadherent patients with schizophrenia are not a homogeneous population and subtypes of nonadherence might exist, but this hypothesis has not been specifically tested.

AIM

To test the hypothesis of subtypes of nonadherence in schizophrenia and schizoaffective disorder.

METHODS

This prospective study included 110 consecutively admitted patients diagnosed with schizophrenia or schizoaffective disorder. Assessments were performed at baseline and at 6 mo follow-up after discharge. Sociodemographic, clinical, psychopathological and treatment-related variables were evaluated. Adherence was defined as the concurrence of adherence to antipsychotic treatment and outpatient follow-up during the six-month period. Adherence to antipsychotic

Data sharing statement: No additional data are available.

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treatment was defined as the concurrence of objective and subjective adherence. Sixty-four patients (58%) fulfilled nonadherence criteria at the end of the follow-up period and were categorized according to their subtype of nonadherence.

RESULTS

In nonadherent patients (n = 64), 32 (50%) fulfilled criteria of intentional nonadherence, and 32 (50%) of unintentional nonadherence (UNA). Unintentional nonadherent patients, as compared to intentional nonadherent patients, are characterized by older age, lower educational level, worse cognitive and negative symptoms, greater severity, worse knowledge of their treatment regimen, greater prevalence of supervision of the treatment, lower number of prior hospitalizations and greater use of nonpsychiatric treatment, anticholinergics and hypnotics. Low educational level (OR = 26.1; 95%CI: 2.819-241), worse treatment knowledge at six months (OR per unit = 0.904; 95%CI: 0.853-0.957) and nonpsychiatric treatment at six months (OR = 15.8; 95%CI: 1.790-139) were independently associated to UNA.

CONCLUSION

Differentiated subtypes of nonadherence according to intentionality seem to exist in patients with schizophrenia and schizoaffective disorder. Our findings suggest the need for differentiated approach, both in future research and in clinical practice.

Key Words: Adherence; Hospitalization; Psychosis; Hypothesis; Unintentional nonadherence; Intentional nonadherence

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Core Tip: Nonadherence is a major problem in the treatment of psychotic disorders. The scarcity of consistently identified variables associated with nonadherence could be due, at least in part, to real heterogeneity among nonadherent patients. Although in recent years the existence of two main subtypes according to intentionality has been hypothesized, no previous studies have specifically tested this hypothesis. This research aimed to fill this gap. We found differentiated profiles in nonadherent patients according to intentionality. Our results support the nonadherence subtypes hypothesis in psychotic disorders.

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INTRODUCTION

Despite important advances in the management of schizophrenia in recent decades, nonadherence is still a frequent phenomenon, around 40% to 50%[1-3]. Unfortunately, there are still few predictive factors of note and the current state of the evidence may be somewhat disheartening for the practicing clinician[4]. To date, the most consistent risk factors for nonadherence include previous nonadherence, poor insight, negative attitude towards treatment and substance abuse[1,4-7].

The heterogeneity of findings related to several risk factors for nonadherence[4] has been regarded as a consequence of the methodologic limitations of most available studies, especially the absence of a valid assessment method[4,8]. Moreover, only recently has there been expert consensus providing a conceptual and operative definition of adherence[3,8,9]. Finally, although prospective studies provide robust findings regarding cause-effect relationships, most studies are cross-sectional[1,4].

Nevertheless, the scarcity of consistently identified correlates[4] could also be due to real heterogeneity among nonadherent patients. Thus, in recent years the existence of two main subtypes has been hypothesized: Intentional and unintentional[9-14].

Intentional nonadherence (INA) has been defined as a conscious patient decision to stop taking medication or to take less medication than prescribed, whereas unintentional nonadherence (UNA) occurs when practical problems or impairments related to having an illness interfere with taking medication[7], thus involving patient-related, environment and treatment-related factors[15], such as forgetfulness[11], suboptimal awareness of their treatment[16], inadequate health literacy[17], mistakes[18] or barriers to access mental health care[19]. However, there are no clear limits between both subtypes, and overlaps and comorbidities exist[12,15,20,21]. Despite its importance, few specific studies on patients with psychoses have been performed[12,13,21]. Identification of subtypes as well as specific reasons for nonadherence would guide towards different types of interventions[13,18,22].

In this context, we performed this prospective study in hospitalized patients diagnosed with schizophrenia or schizoaffective disorder. Hospitalizations are an important event in the course of illness. For its part, nonadherence has been found to be the main reason for admission in 58.6% of patients[23], it is frequent in the months after discharge[24-26] and discharge can be a good time to introduce strategies aimed at improving adherence[27].

Therefore, this study had the following objectives: (1) To evaluate the prevalence of nonadherence at six-months post discharge; and (2) To evaluate the possible subtypes of nonadherence according to intentionality and to determine whether identified subtypes have a differential profile. We hypothesized that two different subtypes according to intentionality would be identified, and these would have a different profile.

MATERIALS AND METHODS

Patients

This naturalistic, observational and 6-mo follow-up prospective study included 110 patients diagnosed with schizophrenia or schizoaffective disorder according to ICD-10 criteria; patients were consecutively admitted to the Acute Patients' Unit of the Insular University Hospital of Gran Canaria, The Canary Islands, Spain, over an 18-mo period since recruitment commenced (February 2017), and whose follow-up was due to take place at the Community Mental Health Unit (CMHU) of Vecindario, which covers a population of 195410 people. As additional inclusion criteria, patients had to be aged over 18 years, understand the information concerning the study and agree to participate. Exclusion criteria were suffering intellectual disability or dementia. Out of 115 eligible patients, 5 (4.35%) refused to participate. This study was carried out in compliance with the latest version of the Declaration of Helsinki and approved by the Ethics Committee of Insular University Hospital of Gran Canaria. All patients were informed about the characteristics of the study and gave their written consent.

Procedure

Baseline evaluation was performed during any of the 7 d prior to discharge. Follow-up assessment was performed 6 mo from discharge. All patients were evaluated by the same psychiatrist. Baseline evaluation included sociodemographic, clinical, psychopathologic and treatment-related variables, which are shown in Tables 1 and 2. Psychopathology was evaluated by the Clinical Global Impression-Schizophrenia Scale (CGI-SCH), severity subscale, validated in Spanish[28], at baseline and follow-up. Insight was evaluated by the first three items of the Amador Insight Scale, which assess general disorder awareness[29], validated in Spanish[30]. Cognitive performance was assessed by means of the SCIP-S scale (Screen for Cognitive Impairment in Psychiatry), validated in Spanish[31].

Treatment-related variables included several objective and subjective measures. Regarding the latter, attitude towards medication was evaluated by the Drug Attitude Inventory (DAI)[32], Spanish validated version[33]. Beliefs about treatment were assessed through the Beliefs about Medicines Questionnaire (BMQ)[34] in its Spanish validated version[35]. Perceptions about shared decisions were evaluated by the 9-item Shared Decision Making Questionnaire (SDM-Q-9) in its Spanish validated version[36].

Knowledge was evaluated by means of an ad hoc questionnaire (Supplementary Material). Treatment knowledge was restricted to that of the main antipsychotic, as considered by the psychiatrist. To avoid potential bias due to the "Hawthorne effect"[37] patients were not informed that their knowledge of treatment, diagnosis and follow-up was to be assessed at 1 h, 2 wk and 6 mo from the time of instruction.

Table 1 Sociodemographic, clinical, and treatment-related characteristics of the sample at admission and differences between unintentional and intentional nonadherent patients

	Total non-adherence (*n* = 64)	Unintentional (*n* = 32)	Intentional (*n* = 32)	*P* value
Age (yr)	40.6 ± 9.6	44.4 ± 10.1	36.8 ± 7.4	0.001
Sex (male)	39 (60.9)	23 (71.9)	16 (50.0)	0.073
Marital status				0.522
Married or stable relationship	12 (18.8)	5 (15.6)	7 (21.9)	
Single, separated, divorced, or widowed	52 (81.2)	27 (84.4)	25 (78.1)	
Educational level				< 0.001
Primary or lower	34 (53.1)	25 (78.1)	9 (28.1)	
Secondary or higher	30 (46.9)	7 (21.9)	23 (71.9)	
Socio-economic level				0.376
Low	49 (76.6)	26 (81.2)	23 (71.9)	
Medium-High	15 (23.4)	6 (18.8)	9 (28.1)	
Employment situation				0.162
Active	5 (7.8)	1 (3.1)	4 (12.5)	
No active	59 (92.2)	31 (96.9)	28 (87.5)	
Cohabitation				0.794
Living with family	41 (64.1)	20 (62.5)	21 (65.6)	
Living alone	23 (35.9)	12 (37.5)	11 (34.4)	
Length of admission (d)	23 (14-32)	25 (14-35)	21 (14-26)	0.179
Length of the disorder (yr)	11 (5-19)	11 (5-20)	10 (6-17)	0.577
Number of previous psychiatric admissions	2.0 (1.0-5.0)	1.0 (1.0-4.0)	3.0 (1.0-5.2)	0.036
Time since last hospitalization (yr)	2.0 (1.1-5.0)	2.0 (1.0-7.3)	2.0 (1.3-3.0)	0.435
ICD diagnosis				0.079
Schizophrenia	35 (54.7)	21 (65.6)	14 (43.8)	
Schizoaffective disorder	29 (45.3)	11 (34.4)	18 (56.2)	
Current substance use or abuse	36 (56.2)	18 (56.2)	18 (56.2)	1
History of substance use or abuse	44 (68.8)	22 (68.8)	22 (68.8)	1
Daily doses (oral antipsychotic)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.243
Psychotropic pills per day	6 (4-8)	6 (4-8)	5 (3-9)	0.479
Attitude towards treatment				0.664
Negative	41 (64.1)	19 (59.4)	22 (68.8)	
Neutral	15 (23.4)	9 (28.1)	6 (18.8)	
Positive	8 (12.5)	4 (12.5)	4 (12.5)	

Data are means ± SD, frequencies (%) and medians (IQR).

Adherence

Adherence was defined as the concurrence of adherence to antipsychotic treatment and outpatient follow-up during the six-month period. Adherence to antipsychotic treatment was defined as the concurrence of objective and subjective adherence.

Objective adherence was defined as taking more than 80% of prescribed medication, as recommended by expert consensus[3]. Medication possession ratio (MPR) was used to assess adherence to oral antipsychotics, and clinical records to assess adherence to

Table 2 Psychopathological, treatment-related, and other characteristics of nonadherent patients during hospitalization and at 6 mo post discharge, and differences between unintentional and intentional nonadherence

	Hospitalization				6 mo			
	Total Nonadherence (*n* = 64)	Unintentional (*n* = 32)	Intentional (*n* = 32)	*P* value	Total nonadherence (*n* = 64)	Unintentional (*n* = 32)	Intentional (*n* = 32)	*P* value
Amador insight scale, general disorder awareness	11 (9-15)	11 (9-15)	11 (9-15)	0.634	9 (9-11)	9 (6-11)	9 (9-13)	0.467
Mental disorder	5 (3-5)	5 (3-5)	5 (3-5)	0.750	3.0 (3.0-5.0)	3.0 (2.0-4.5)	3.0 (3.0-5.0)	0.177
Effects of the medication	3.0 (3.0-5.0)	3.0 (3.0-5.0)	3.0 (3.0-5.0)	0.638	3.0 (2.0-3.0)	3.0 (2.2-3.0)	3.0 (2.5-4.0)	0.907
Social consequences	3.0 (3.0-5.0)	3.0 (3.0-5.0)	4.0 (3.0- 5.0)	0.441	3.0 (2.0-5.0)	3.0 (2.2-4.8)	3.0 (2.5-5.0)	0.861
CGI-SCH severity. Total score	11 (10-13)	11 (10-13)	10 (9-12)	0.086	10 (9-12)	12 (10-13)	9 (8-10)	0.003
Psychotic symptoms	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (3.0- 3.0)	0.645	2.0 (2.0- 3.0)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	0.118
Negative symptoms	2.0 (1.0-2.2)	2.0 (1.0-2.2)	2.0 (1.0-2.2)	0.186	2.0 (1.0-2.0)	2.0 (2.0-3.0)	2.0 (1.0-2.0)	< 0.001
Depressive symptoms	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.413	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.346
Cognitive symptoms	2.0 (1.0-2.0)	2.0 (2.0-2.0)	1.0 (1.0-2.0)	< 0.001	2.0 (1.0-2.0)	2.0 (2.0-2.8)	1.0 (1.0-2.0)	< 0.001
Global severity	3.0 (3.0-3.0)	3.0 (3.0- 3.0)	3.0 (2.8-3.0)	0.679	3.0 (2.0-3.0)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	0.210
SCIP. Total score	49 (40-55)	42 (32-52)	52 (46-59)	0.002	48 (41-59)	42 (33-49)	56 (48-62)	< 0.001
Verbal learning-immediate	13 (10-15)	12 (9-15)	13 (11-15)	0.073	15 (11-17)	13 (10-16)	15 (12-18)	0.032
Working memory	16 (13-20)	14 (11-18)	18 (16-21)	0.004	17 (14-20)	14 (12-17)	19 (17-20)	0.001
Verbal fluency	10 (8-13)	10 (7-11)	12 (9-14)	0.022	11 (8-12)	10 (7-11)	11 (8-13)	0.045
Verbal learning-delayed	4.0 (2.0-5.0)	3.0 (2.0-4.0)	4.0 (3.0-5.0)	0.003	4.0 (3.0-5.0)	3.0 (1.2-4.0)	5.0 (4.0-6.0)	< 0.001
Processing speed	4.0 (3.0-6.0)	3.0 (2.0-5.0)	5.0 (3.0-7.0)	0.004	4.0 (3.0-5.0)	3.0 (2.0-4.0)	5.0 (4.0-6.0)	< 0.001
Type of antipsychotic treatment				0.114				0.114
Oral	22 (34.4)	8 (25.0)	14 (43.8)		22 (34.4)	8 (25.0)	14 (43.8)	
Injectable or injectable + oral	42 (65.6)	24 (75)	18 (56.2)		42 (65.6)	24 (75)	18 (56.2)	
Supervision of the treatment	40 (65.6)	21 (67.7)	19 (63.3)	0.717	51 (79.7)	29 (90.6)	22 (68.8)	0.03
SDM-Q-9. total score	17 (9-23)	10 (8-19)	20 (11-30)	0.010	18 (11-21)	17 (10-21)	18 (14-22)	0.235
BMQ, beliefs about medicines, general	22 (18-27)	22 (20-27)	22 (17-25)	0.509	22 (18-26)	22 (18-26)	22 (16-25)	0.623
BMQ, beliefs about medicines, specific	6 (5-7)	6 (6-7)	6 (5-7)	0.142	31 (26-34)	31 (27-35)	30 (26-34)	0.479
DAI	3.0 (-3.0-7.0)	3.0 (-1.0-5.0)	1.0 (-3.0-7.0)	0.914	1.0 (-3.0-3.0)	1.0 (-3.0-6.5)	1.0 (-3.0-3.0)	0.374
Morisky-Green test	2.0 (2.0-3.0)	2.0 (1.8-2.2)	2.0 (2.0-3.0)	0.302	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.5 (2.0-3.0)	0.084

BARS	100 (100-100)	100 (100-100)	100 (100-100)	0.329	55 (30-74)	60 (20-78)	50 (40-70)	0.586
Knowledge of the treatment at 1 h[1]	75 (58-92)	67 (58-75)	83 (75-92)	< .001				
Knowledge of the treatment at 20 d[1]	79 (62-92)	65 (42-77)	83 (81-92)	< .001				
Knowledge of the treatment at 6 mo[1]					80 (60-90)	60 (40-70)	90 (80-100)	< 0.001

Data are means ± SD, frequencies (%) and medians (IQR).

[1]There were 3 lost cases regarding knowledge of the treatment (n = 61; unintentional, n = 30; intentional, n = 31). Knowledge of the treatment: Knowledge of the treatment, diagnosis, and follow-up from the time of instruction. The values represent means of percentages. BMQ: Beliefs about medicines questionnaire; CGI-SCH: Clinical Global Impression–Schizophrenia; IQR: Inter-quartile range; SCIP: Screen for Cognitive Impairment in Psychiatry; SDM-Q-9: Shared Decision Making Questionnaire; SD: Standard deviation; DAI: Drug attitude inventory; BARS: Brief adherence rating scale.

long-acting injectables (LAI). The MPR is a ratio of total days' supply to number of days of study participation per participant[38], and were calculated by each patient by dividing the number of outpatient days' supply of medication the patient received during the study period by the number of days' supply they needed to receive if they were taking their outpatient medication continuously, as previously done[39]. When there were two or more oral antipsychotics, the mean of the respective MPR was obtained. Regarding LAI, correct administration was considered as a dose administered within three days of the scheduled dose, as performed previously[10].

Subjective adherence was defined as a score of 3 or 4 in the Morisky-Green test, as performed previously[40,41] and a score higher than 80% on the BARS scale at six months. The BARS is a 4-item scale specifically developed to measure adherence to antipsychotics in schizophrenia[42].

Adherence to outpatient follow-up was defined as the concurrence of attendance at scheduled visits greater than 80% (after excluding justified absences) and the absence of dropout, defined as nonattendance at scheduled visits for at least six months.

Therefore, nonadherence was defined as the occurrence of nonadherence to antipsychotic treatment, nonadherence to outpatient follow-up, or both. For its part, nonadherence to antipsychotic treatment was defined as the occurrence of objective nonadherence, subjective nonadherence or both.

Subtypes of nonadherence

Subtypes were assigned at 6 mo follow-up, after clinical assessment, information from the CMHU therapeutic team, details of medical record, and interview of family members when needed. Based on extensive literature reviews[14,43], we established a set of reasons for nonadherence. Patients were assigned to UNA if the main reason was any of items 2, 4, 7 or 8, and to INA for the remaining reasons. When there were two or more reasons for nonadherence, these were also recorded for descriptive purposes. The reasons included: (1) The patient does not believe in the need for treatment; (2) Forgetfulness; (3) To minimize or to avoid possible adverse effects; (4) Misunderstanding; (5) To minimize or to avoid possible risk of addiction; (6) To make the regimen more acceptable in order to fit with their daily schedule; (7) Regimen complexity; (8) Financial reasons and/or accessibility problems; (9) To see what happens without treatment; (10) Replacing medicines with non-pharmacological treatments; (11) Poor therapeutic alliance; and (12) To avoid stigma associated to antipsychotics.

Statistical analysis

Categoric and continuous variables were expressed respectively as frequencies and percentages and as mean and standard deviation (SD) when data followed a normal distribution, or as median and interquartile range (IQR = 25th-75th percentile) when distribution departed from normality. Percentages were compared, as appropriate, using Chi-square (χ^2) test or exact Fisher tests; means and medians were compared by the student t-test and Wilcoxon test for independent data, respectively. In order to identify factors that maintain independent association with each outcome (nonadherence; unintentional subgroup), a multivariate logistic regression analysis was performed. Variables that revealed statistically significant association with the corresponding outcome in univariate analysis were entered into the multivariate analysis. Variables based on the best subset regression and Akaike information

criterion were then selected. Models were summarized as coefficients (SE), *P* values (likelihood ratio test) and odds-ratio, which were estimated by means of 95% confidence intervals. Statistical significance was set at $P < 0.05$. Data were analyzed using the R package, version 3.3.1.[44]. The statistical review of the study was performed by a biomedical statistician.

RESULTS

Nonadherence and characteristics of the sample

We recruited 110 patients, of whom 64 (58%) fulfilled nonadherence criteria; 56.4% nonadherence to antipsychotic treatment, and 20.9% nonadherence to outpatient follow-up. Since this study is focused on evaluation of possible subtypes of nonadherence, the total sample was comprised of nonadherent patients ($n = 64$). The percentage of men (60.9%) was higher than that of women, and mean age was 37.4 years. The most common diagnosis was schizophrenia (54.7%), the length of the psychiatric disorder showed a median of 11 years, the length of admission was 23 d, and prevalence of current substance use or abuse was high (56.2%). Sociodemographic, clinical, psychopathologic and treatment-related variables are shown in Tables 1 and 2.

Subtypes and subgroups of nonadherence

In nonadherent patients ($n = 64$), 32 (50%) fulfilled criteria of INA, and 32 (50%) of UNA. The prevalence of the main reasons identified in INA patients was: The patient does not believe in the need for treatment (75%), to minimize or to avoid possible adverse effects (18.8%), to make the regimen more acceptable in order to fit with their daily schedule (3.1%), to see what happens without treatment (3.1%). The prevalence of the main reasons identified in UNA patients was: Forgetfulness (65.6%), financial reasons and/or accessibility problems (15.6%), misunderstanding (12.5%), regimen complexity (6.3%). Mixed reasons (*i.e.*, concurrence of two or more reasons, belonging to both INA and UNA) were found in 42.2% of the patients.

Variables associated with nonadherence subgroups

UNA patients, as compared to INA patients, showed older age (44.4 *vs* 36.8 respectively, $P < 0.001$), higher prevalence of low educational level (78.1% *vs* 28.1%, $P < 0.001$), lower number of prior hospitalizations (1.0 *vs* 3.0, $P = 0.036$), greater severity at six months (12 *vs* 9, $P = 0.003$), worse negative symptoms at 6 mo (2 *vs* 2, $P < 0.001$), worse cognitive symptoms at admission and at 6 mo, as assessed both by the CGI (2 *vs* 1 respectively, $P < 0.001$) and the SCIP (42 *vs* 56, $P < 0.001$), worse knowledge of the treatment regimen at 1 h (67 *vs* 83, $P < 0.001$), at 20 d (65 *vs* 83, $P < 0.001$), and at 6 mo (60 *vs* 90, $P < 0.001$), greater prevalence of supervision of the treatment (90.6% *vs* 68.8%, $P = 0.03$), greater use of anticholinergics at admission (35.5% *vs* 12.5%, $P = 0.032$) and at six-month follow-up (35.5% *vs* 12.5%, $P = 0.032$), hypnotics at admission (90% *vs* 71.9%, $P = 0.055$), and nonpsychiatric treatment at admission (60% *vs* 25%, $P = 0.005$) and at 6 mo (60% *vs* 25%, $P = 0.005$).

Tables 1 and 2 summarize the sociodemographic, clinical, psychopathologic and treatment-related differences between unintentional and intentional nonadherent patients. The multivariate logistic regression model for nonadherence according to subgroups is shown in Table 3. Factors that revealed an independent association with UNA were nonpsychiatric treatment at six months (OR = 15.8; 95%CI: 1.790-139), low educational level (OR = 26.1; 95%CI: 2.819-241), and treatment knowledge at six months (average) (OR per unit = 0.904; 95%CI: 0.853-0.957).

DISCUSSION

Nonadherence in the post discharge period was high. Up to 58% of patients did not fulfil adherence criteria at six-month follow-up. This high rate is consistent with that found in other prospective studies using electronic monitoring devices. Thus, nonadherence rates were 48% at 3 mo[45] and 62.7% at six months from discharge[26]. In addition to the alarming high rate of nonadherence, identification of distinguishable profiles of nonadherent patients according to their intentionality was the main finding of this study. Our findings are consistent with the hypothesis regarding the existence of nonadherence subtypes according to intentionality[9-14] and, therefore, support this hypothesis.

Table 3 Variables associated with nonadherence according to intentionality after multivariate logistic regression (reference: Unintentional nonadherence)

	P value[1]	AIC[2]	Odds ratio (95%CI)
Low educational level	< 0.001	52.1	26.1 (2.819; 241)
Non-psychiatric treatment at 6 mo	0.003	47.7	15.8 (1.790; 139)
Treatment knowledge at 6 mo, mean	< 0.001	64.9	0.904 (0.853; 0.957)

[1]Likelihood ratio test.
[2]If the variable is removed. AIC for the full model = 41.1; AIC is a measure of lack of fit. The removal of any variable leads to a model with more lack of fit.
AIC: Akaike information criterion.

Worse negative symptoms and cognitive deficits were associated with UNA patients. Persistent negative symptoms[3,46] and cognitive symptoms[7,47] can affect the ability to manage medications. Cognitive deficits may hinder understanding the treatment regimen, its awareness as well as the organizational capacity needed for adherence, particularly with complex regimens[7,48]. In this regard, nonpsychiatric treatment at six months was strongly and independently associated with UNA patients in this study. However, the relationship between cognition and nonadherence is still inconclusive[4]. This heterogeneity of findings may have been influenced by methodologic difficulties and by the fact that the impact of cognitive deficits likely depends on other conditions and circumstances, such as whether or not there is good family support involved in planning and monitoring medication intake[7]. Nevertheless, an additional factor may be the hypothesized heterogeneity of nonadherent patients. According to this hypothesis, cognitive deficits could be relevant only or especially for UNA. To the best of our knowledge, this is the first study that specifically assesses the association between cognitive features and different nonadherence subtypes.

For its part, knowledge of treatment, diagnosis and follow-up was lower in UNA at the three time points assessed. In addition, worse knowledge of the treatment regimen at six months was independently associated with this subtype. This area remains little studied. Most studies have found suboptimal knowledge of the treatment[16,49,50]. Moreover, physicians have been found to overestimate understanding the treatment by their patients[51]. Some authors have found an association between knowledge of the purpose for taking medication and adherence, but not with other aspects[49], while others have not found such an association[50]. This disparity of findings may have been influenced by methodologic issues, such as the absence of a uniform description of what adequate knowledge of treatment is and absence of operational definitions; or again, by a real heterogeneity within nonadherent patients, as we hypothesize. To the best of our knowledge, this is the first study that specifically assesses the association between knowledge of the treatment and different nonadherence subtypes.

Lower educational level and older age were found to be associated with UNA patients. In addition, educational level was independently associated with this subtype. Most studies have not found an association between educational level and adherence[1,3,4]. Nevertheless, when considering the possible subtypes of nonadherence, it seems plausible that a lower educational level may contribute to inadequate understanding of treatment regimen, and this in turn may lead to UNA. In this context, in a study on community-dwelling seniors admitted to acute medicine services, inadequate and marginal health literacy patients were likely to have UNA, whereas those with adequate health literacy were more likely to have INA[17]. Future studies that assess the possible association between educational level and UNA in schizophrenia would shed light on this issue. With regard to age, this variable has also yielded contradictory results. Whereas some studies have found younger age associated with adherence problems[3,52], others have failed to find such an association[1,10].

Finally, neither insight nor any of its three basic components were associated with different subtypes of nonadherence. This finding contrasts with the notion that poor insight is an important reason for INA[7], or specifically a risk factor likely to affect willingness to take medication[3,53]. It is likely that this absence of differences has been influenced by the fact that the global sample of nonadherent patients showed poor insight. This finding was to be expected, since our sample consisted of admitted patients evaluated both during hospitalization and at follow-up. Another factor may

be that we found mixed reasons in 42.2% of the patients, which is consistent with the notion that overlapping between both subgroups seems to exist[11,12,20,21]. In any case, although poor insight is an unquestionable risk factor for nonadherence[1,3,5,10,54], the role of insight in intentional *vs* unintentional adherence has not been sufficiently studied.

This study has certain limitations and strengths. The assessment method of adherence was not the reference standard, *i.e.*, electronic monitoring[55-57]. However, this method is an indirect measure of treatment adherence and also has drawbacks[7,58], and we have combined objective and subjective methods from multiple sources to assess adherence, as recommended[3,4,7,59]. Moreover, we worked in accordance with the operational criteria for nonadherence recommended in the expert consensus[3]. Furthermore, one of the scales used to assess adherence has revealed similar estimates of adherence to those produced by electronic monitoring[42]. Unfortunately, intentional and unintentional dimensions of patient medication taking are poorly categorized within adherence literature[60]. Thus, there is neither consensus regarding the differentiation of these subtypes nor standardized instruments to assess them. Finally, the modest sample size and the nature of the sample may affect both the statistical power and the generalizability of our findings. The main strengths of this study are its prospective design - which confers strength in the establishment of cause-effect relationships - and a wide evaluation of variables including subjective aspects, treatment-related variables and knowledge of the treatment, usually neglected in the literature.

CONCLUSION

In conclusion, we have found differentiated profiles among nonadherent patients according to intentionality. UNA patients, as compared to INA patients, are characterized by lower educational level, worse knowledge of their treatment regimen, worse cognitive and negative symptoms, older age, greater use of nonpsychiatric treatment, and fewer prior hospitalizations, as most prominent features. These findings support the hypothesis that there are nonadherence subtypes in patients with psychotic disorders, and suggest the need for a differentiated approach, both in future research and clinical practice.

ARTICLE HIGHLIGHTS

Research background

Despite important advances in the management of schizophrenia in recent decades, nonadherence remains a common phenomenon, with prevalence rates of approximately 40%-50%. The heterogeneity of findings regarding several risk factors for nonadherence could also be due to real heterogeneity among nonadherent patients.

Research motivation

The existence of two main subtypes according to intentionality has been hypothesized: Intentional and unintentional. Identification of subtypes as well as specific reasons for nonadherence would provide guidance in terms of different types of interventions.

Research objectives

To evaluate possible subtypes of nonadherence according to intentionality and to determine whether identified subtypes show a differential profile.

Research methods

This naturalistic, observational, and 6-mo follow-up prospective study included 110 admitted patients diagnosed with schizophrenia or schizoaffective disorder. Baseline evaluation included sociodemographic, clinical, psychopathologic and treatment-related variables. Adherence was defined as the concurrence of adherence to antipsychotic treatment and outpatient follow-up during the six-month period. Adherence to antipsychotic treatment was defined as the concurrence of objective and subjective adherence. Subtypes were assigned at 6 mo follow-up based on a set of reasons for nonadherence.

Research results

Sixty-four patients (58%; n = 64) fulfilled nonadherence criteria at the end of the follow-up period and were categorized according to subtype of nonadherence: 32 (50%) fulfilled criteria of intentional nonadherence, and 32 (50%) unintentional nonadherence (UNA). Several variables were independently associated with UNA: Low educational level (OR = 26.1; 95%CI: 2.819-241), worse treatment knowledge at six months (OR per unit = 0.904; 95%CI: 0.853-0.957) and nonpsychiatric treatment at six months (OR = 15.8; 95%CI: 1.790-139).

Research conclusions

This study specifically tests the subtypes hypothesis in psychotic disorders. We found two subtypes of nonadherence according to intentionality, as well as differentiated profiles. Our results support the nonadherence subtypes hypothesis in psychotic disorders.

Research perspectives

We propose some directions for future research: (1) Replication studies to confirm the existence of differentiated subtypes of nonadherence in psychotic disorders; and (2) If confirmed, adoption of a differentiated approach, both in future research and clinical practice.

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META-ANALYSIS

Effects of smartphone-based interventions and monitoring on bipolar disorder: A systematic review and meta-analysis

Jia-Yuan Liu, Kang-Kang Xu, Guang-Lin Zhu, Qi-Qi Zhang, Xiao-Ming Li

ORCID number: Jia-Yuan Liu 0000-0002-8764-7186; Kang-Kang Xu 0000-0002-8712-4481; Guang-Lin Zhu 0000-0002-7383-5741; Qi-Qi Zhang 0000-0002-4117-0124; Xiao-Ming Li 0000-0002-5228-1372.

Author contributions: Li XM conceived and guided the study; Liu JY and Shao WJ carried out the literature searches; Liu JY and Xu KK extracted the data; Zhu GL and Li XM assessed the study quality; Liu JY, Xu KK, and Li XM performed the statistical analysis; Liu JY wrote the manuscript; Xu KK, Zhu GL, Shao WJ, and Zhang QQ revised the manuscript.

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Jia-Yuan Liu, Xiao-Ming Li, Department of Medical Psychology, Chaohu Clinical Medical College, Anhui Medical University, Hefei 230032, Anhui Province, China

Jia-Yuan Liu, Department of Anesthesia, First Clinical Medical College, Anhui Medical University, Hefei 230032, Anhui Province, China

Kang-Kang Xu, Guang-Lin Zhu, Department of Clinical Medicine, Second Clinical Medical College, Anhui Medical University, Hefei 230032, Anhui Province, China

Qi-Qi Zhang, Department of Clinical Medicine, First Clinical Medical College, Anhui Medical University, Hefei 230032, Anhui Province, China

Corresponding author: Xiao-Ming Li, PhD, Adjunct Professor, Department of Medical Psychology, Chaohu Clinical Medical College, Anhui Medical University, No. 81 Meishan Road, Shushan District, Hefei 230032, Anhui Province, China. psyxiaoming@126.com

Abstract

BACKGROUND

Recently, there has been a range of studies about smartphone-based interventions and monitoring for reducing symptoms of bipolar disorder (BD). However, their efficacy for BD remains unclear.

AIM

To compare the effect of smartphone-based interventions and monitoring with control methods in treating patients with BD.

METHODS

A systematic literature search was performed on PubMed, Embase, Clinical trials, psycINFO, Web of Science, and Cochrane Library. Randomized clinical trials (RCTs) or single-group trials in which smartphone-based interventions and monitoring were compared with control methods or baseline in patients with symptoms of BD were included. Data were synthesized using a random-effects or a fixed-effects model to analyze the effects of psychological interventions and monitoring delivered *via* smartphone on psychiatric symptoms in patients with BD. The primary outcome measures were set for mania and depression symptoms. Subgroups were created to explore which aspects of smartphone interventions are relevant to the greater or lesser efficacy of treating symptoms.

RESULTS

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We identified ten articles, including seven RCTs (985 participants) and three single-group trials (169 participants). Analysis of the between-group study showed that smartphone-based interventions were effective in reducing manic [g = -0.19, 95% confidence interval (CI): -0.33 to -0.04, $P = 0.01$] and depressive (g = -0.28, 95%CI: -0.55 to -0.01, $P < 0.05$) symptoms. In within-group analysis, smartphone-based interventions significantly reduced manic (g = 0.17, 95%CI: 0.04 to 0.30, $P < 0.01$) and depressive (g = 0.48, 95%CI: 0.18 to 0.78) symptoms compared to the baseline. Nevertheless, smartphone-based monitoring systems significantly reduced manic (g = 0.27, 95%CI: 0.02 to 0.51, $P < 0.05$) but not depressive symptoms. Subgroup analysis indicated that the interventions with psychoeducation had positive effects on depressive (g = -0.62, 95%CI: -0.81 to -0.43, P < 0.01) and manic (g = -0.24, 95%CI: -0.43 to -0.06, $P = 0.01$) symptoms compared to the controlled conditions, while the interventions without psychoeducation did not ($P > 0.05$). The contacts between therapists and patients that contributed to the implementation of psychological therapy reduced depression symptoms (g = -0.47, 95%CI: -0.75 to -0.18, $P = 0.01$).

CONCLUSION

Smartphone-based interventions and monitoring have a significant positive impact on depressive and manic symptoms of BD patients in between-group and within-group analysis.

Key Words: Smartphone; Bipolar disorder; Monitoring; Interventions; Meta-analysis; Systematic review

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Core Tip: To date no study has used meta-analysis to pool the existing evidence to examine the efficacy of smartphone-based interventions and monitoring for bipolar disorder. This is the first systematic review and meta-analysis investigating the effects of interventions and monitoring delivered *via* smartphone on bipolar disorder.

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INTRODUCTION

Bipolar disorder (BD) is a serious mood disorder that is characterized by depressive, manic, and mixed episodes[1]. It is estimated that the lifetime prevalence of BD is 1.0% for bipolar disorder I and 1.1% for bipolar disorder II[2]. Patients who do not receive adequate and appropriate treatment are then at risk for experiencing plentiful social and occupational impairments, even suicidal behavior[3].

Fortunately, many available treatments aim to cure manic or depressive episodes and stabilize mood[4]. However, there is a range of obstacles towards professional BD treatment. The transportation of mental health services and high-quality medications make treatment unaffordable[5]. Additionally, medication and psychotherapy are not acceptable to some patients who are ashamed of receiving treatment for mood disorder, so the therapeutic effectiveness is limited[6,7]. Therefore, innovative methods of treatment are urgently needed.

Digital technology may represent a feasible and novel solution. The majority of adults own smartphones. In recent years, the number of smartphone users has continually increased[8]. Additionally, using smartphones as a tool for psychological treatment is well-accepted for most people because it is cost-effective[9]. Use of smartphone also breaks the limitation of distance between patients and therapists, therefore it is a viable method to apply smartphones to treat someone who has difficulty in accessing health care[10]. Meanwhile, privacy and individuation are

guaranteed in the use of smartphones so that treatment acceptance and compliance are enhanced[11]. Therefore, people can accept smartphone-based interventions at any time they want.

This promising therapeutic potential of smartphones has aroused the interest of different organizations such as governments, advocacy groups, technology companies, and research groups internationally[12,13]. Recently, there has been a range of articles[14-23] about smartphone mental health interventions used for reducing symptoms of BD. Although the idea of smartphone use in health care is becoming more popular, it is difficult to separate actual efficacy from overstated aspirational claims. With thousands of mental disorder treatments readily available, it is urgent to find strong evidence to prove it useful, making sure that people have an understanding of smartphone-based interventions for BD.

Recent meta-analyses have suggested that smartphone interventions can have a positive impact on physical diseases, such as diabetes[24]. Also, the efficacy of smartphone interventions for a series of mood disorders is explained with recent meta-analyses, such as depression, anxiety, and post-traumatic stress disorder[25-27]. To date, no study has used meta-analysis to pool the existing evidence to examine the efficacy of smartphone interventions for BD. Moreover, there are three reviews related to the smartphone monitoring systems collecting data to predict severity of symptoms[28-30]. However, the clinical effect of the smartphone-based monitoring system on symptoms of BD patients has yet to be established. More recently, several single-group trials are relevant to the effectiveness of the smartphone-based intervention for BD. However, no systematic review and meta-analysis has examined the efficacy of the smartphone-based intervention and monitoring for symptoms in single-group trials. Nevertheless, there is evidence that the estimates from high-quality single-group trials can overcome the paucity of prospective randomized evidence. The estimated results may be similar to those of randomized controlled trials (RCTs). Pooling of high-quality single-group trials may be as accurate as pooling of RCTs[31-34].

We conducted the present meta-analysis to provide the first overall estimated effects of smartphone-based interventions and monitoring for reducing symptoms in BD patients. We conducted between-group analyses using the data extracted from the RCTs. We also performed within-group analyses of RCTs and single-group trials. Subgroups were created to explore which aspects of smartphone interventions are relevant to the greater or lesser efficacy of treating symptoms.

MATERIALS AND METHODS

This review and meta-analysis followed the PRISMA statement for the transparency and comprehension of the methodology and results reporting[35]. The PROSPERO ID of this meta-analysis is CRD42018092539.

Literature search

We searched PubMed, Embase, Clinical trials, psycINFO, Web of Science, and Cochrane Library from 1993 to August 1, 2019. In the case of any other eligible studies, we looked up reference lists of related reviews and articles. Besides, key researchers in this field were asked whether they knew about unpublished trials.

Study selection

The included studies fulfilled the following criteria: (1) All articles in English language; (2) Patients with a diagnosis of BD. Nevertheless, participants with BD and other types of mood disorders that had no influence on the cure of BD at the same time were also included; (3) Intervention: Website, smartphone-based apps, instruction of therapists *via* smartphone to facilitate psychotherapy; (4) RCTs and single-group studies; and (5) Outcomes: Reported either mania or depression symptom severity scores before and after intervention. The exclusion criteria were: (1) The intervention was not clearly defined; (2) Specific outcomes were not reported; (3) Unavailability of full text; and (4) Studies investigating the feasibility and satisfaction of smartphone-based intervention.

Two authors (Jia-Yuan Liu and Kang-Kang Xu) selected the articles according to the inclusion criteria after retrieval and screening of the relevant citations in full text. To identify the applicable articles, they read the abstracts and titles. A third reviewer resolved any disagreement that emerged in the process of searching and selection. The procedure of specific inclusion and extraction is shown in Figure 1.

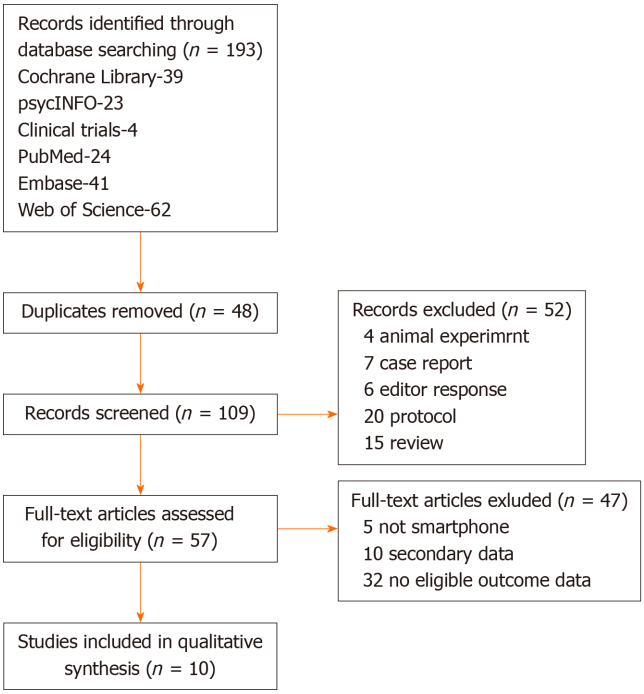


Figure 1 Study selection.

Data extraction

An extraction form was used for each article to collect the following data: (1) Participant information: Sample size, mean age, inclusion criteria, and diagnosis; (2) Study design: Trial quality, whether controlled or not; (3) Smartphone intervention: Study duration, details of intervention, and frequency of intervention; and (4) Effects on mania and depression: Changes in total depressive and manic symptoms scored before and after interventions using any clinically validated rating scale.

Risk of bias

The Cochrane risk of bias assessment tool was used for assessment of the RCT methodological quality. Bias risk in each domain of selection, performance, detection, attrition, and reporting ranking as high, low, or unknown was assessed independently by two reviewers. And inconsistencies were resolved through discussion. For publication bias, it was inappropriate to make a funnel plot to determine it because the number of included trials was no more than 10[36]. We did not have enough studies to make a meaningful funnel plot that was proposed by Egger *et al*[37].

Statistical analysis

Statistical analyses were performed with Review Manager version 5.3 (free software downloaded from http://www.cochrane.org). Between-group analysis was conducted for RCTs. The differences in changes in manic and depressive symptoms between smartphone-based intervention and control groups were pooled for calculation of the overall effect size using Hedges' g[38] with 95% confidence intervals (CIs). We conducted heterogeneity tests among these studies. In case of $I^2 > 50\%$ and $P \leq 0.05$, which indicated the presence of high heterogeneity, we chose a random-effects model; otherwise, we used a fixed-effects model. We next implemented within-group effect size of smartphone-based interventions and monitoring on manic and depressive symptoms. We computed Hedges' g statistic as the estimate of within-group effect size for changes from pre- to post-treatment with RCTs and the single-group trials. Lastly, we conducted subgroup analyses to investigate the different effects of components of smartphone-based interventions.

RESULTS

Study selection

A total of 193 articles were retrieved. Eighty-four duplicate articles were excluded. After reading the abstract and title of the remaining 109, we removed 52 case reports, editor responses, reviews, and studies that included animal experiments. Full versions were retrieved for 57 papers, of which ten met eligibility criteria, including seven RCTs and three single-group trials.

Characteristics of included studies

Table 1 displays the full details of the included studies. Available data were extracted from seven RCTs with two arms[15-19,21] or three arms[22] and three trials with single arms[14,20,23]. All but five articles had graphically reported data, which were extracted with graphical digitizer (Get Data Graph Digitizer) from the reported figures[14,18,19-21]. Two of the ten eligible studies included patients with BD and patients with other mood disorders[15,21]. Eight studies included only participants with BD diagnosed according to DSM or ICD-10[14,16-20,22,23]. The mean age of the sample ranged from 16 to 59 years (median, 38 years). Three studies were related to monitoring systems[14,18,19]. Three articles highlighted the heterogeneity in the analysis of the depressive symptoms[14,18,19]. The smartphone interventions and monitoring lasted from 4 wk to 12 mo. Manic and depressive symptoms were measured as an outcome in ten articles.

Risk of bias assessment

The results from the Cochrane Risk of Bias assessment are displayed in Figure 2. The most frequent risk factor for bias was inadequate blinding of participants and personnel with only five of seven studies using the blinding method for which the participants would not be aware of their treatment or control status, as well as the hypothesized outcomes of the trial.

Between-group effect sizes of smartphone interventions on manic and depressive symptoms

The pooled effect size of smartphone-based interventions on manic symptom changes in comparison to control conditions is shown in Figure 3A. Meta-analysis indicated a positive effect size of smartphone-based interventions for reducing manic symptoms compared to control groups (k = 6, n = 785, g = -0.19, 95%CI: -0.33 to -0.04, P = 0.01, I^2 = 0). There was no heterogeneity across the studies, therefore, we chose a fixed-effects model. Smartphone-based interventions were significantly more efficacious than control conditions in improving depressive symptoms (k = 8, n = 985, g = -0.28, 95%CI: -0.55 to -0.01, P < 0.05, I^2 = 75%) (Figure 3B). We found high heterogeneity among the studies. Therefore, sensitivity analyses were conducted to explore the reasons for this high heterogeneity. After excluding one article[18], the heterogeneity was lower, while the pooled effect size was still significant (k = 6, n = 863, g = -0.38, 95%CI: -0.61 to -0.14, P < 0.01, I^2 = 63%).

Within-group effect sizes of smartphone-based interventions on manic and depressive symptoms

In within-group analysis, comparing changes from baseline to post-treatment scores, smartphone-based interventions resulted in significant improvements in manic symptoms (k = 8, n = 914, g = 0.17, 95%CI: 0.04 to 0.30, P < 0.01, I^2 = 0) (Figure 4A). Heterogeneity did not exist, and the fixed-effects model was chosen. In within-group analysis, smartphone-based interventions significantly reduced depressive symptoms (k = 11, n = 1154, g = 0.48, 95%CI: 0.18 to 0.78, I^2 = 81%) after the interventions (Figure 4B). High heterogeneity across article data was found. Therefore, sensitivity analyses were conducted to examine the reasons for the high heterogeneity. After removing two articles[14,21], the heterogeneity was lowered, whereas the effect size was still significant (k = 9, n = 932, g = 0.25, 95%CI: 0.10 to 0.39, I^2 = 15%).

Within-group effect sizes of smartphone-based monitoring on manic and depressive symptoms

In order to investigate whether monitoring *via* smartphone had positive effects on manic and depressive symptoms, we performed within-group analyses. Smartphone-based monitoring appeared effective for manic symptoms (k = 3, n = 257, g = 0.27, 95%CI: 0.02 to 0.51, P < 0.05, I^2 = 0) compared with changes from baseline to post-treatment scores (Figure 5). The pooled effect size from smartphone-based monitoring

Table 1 Characteristics of included studies

Ref.	Sample type	*n*	Age (yr)	Female	Study design	Design	Measure	Smartphone intervention details
Depp *et al*[17]	Outpatient diagnosed with BD	41, 41	47.5	58.50%	RCT	10 wk of PRISM (self-management and monitoring app) *vs* paper and pencil monitoring	YMRS, MADRS	Mood monitoring and self-management APP
Faurholt-Jepsen *et al*[18]	BD patients previously treated for affective disorder	85, 44	43.1	88.40%	RCT	9 mo of MONARCA II (monitoring app) *vs* controlled conditions	YMRS, HDRS	Self-monitoring APP
Ben-Zeev, *et al*[15]	People with mental illness	75, 74	49	41%	RCT	3 mo of FOCUS (self-management app) *vs* clinical treat	PSYRATS, BDI-II	App and phone call from specialist to facilitate APP use
Faurholt-Jepsen *et al*[19]	Outpatients diagnosed with BD	33, 34	29.3	67.10%	RCT	6 mo of MONARCA (self-monitoring app) *vs* Controlled conditions	YMRS, HAMD-17	Self-monitoring APP
Gliddon *et al*[22]	Participants with bipolar disorder	96, 95, 87	39.5	82%	RCT	9 mo of Mood Swings 2.0 *vs* control conditions	YMRS, MADRS	Mood Swing is a web site
Celano, *et al*[16]	BD patients with an acute depressive episode	14, 11	45	68%	RCT	4 wk of telephone-based positive psychology *vs* the control group	None, QIDS-SR	Phone call from specialist to instruct the self-management
Kilbourne, *et al*[21]	People with unipolar and bipolar disorder	115, 123	41.3	66%	RCT	12 mo of CCM (psychosocial intervention) *vs* usual care from provider	None, PHQ-9	Phone call from care manager to facilitate the psychosocial intervention
Depp *et al*[23]	Outpatients with bipolar disorder	10	41	/	Single-group trials	2 wk of PRISM (monitoring and self-management app)	YMRS, MADRS	Mood monitoring and self-management APP
Beiwinkel, *et al*[14]	Outpatients with bipolar disorder	14	47.2	38%	Single-group trials	12 mo of a smartphone-based monitoring system	YMRS, HAMD	Monitoring APP
Miklowitz *et al*[20]	Patients with bipolar disorder	19	37.2	68.40%	Single-group trials	4 mo of FIMM (psychoeducation and monitoring)	YMRS, QIDS-SR	Monitoring and self-management APP

BD: Bipolar disorder; RCT: Randomized clinical trial; ASRM: Altman self-rating mania; APP: Application; BDI: Beck depression inventory; BHS: Beck hopelessness scale; HAMD-17: 17-item hamilton depression rating scale; HRSD: Hamilton rating scale for depression; MADRS: Montgomery–Asberg depression rating scale; PHQ-9: Nine-item patient health questionnaire; PSYRATS: Psychotic symptom rating scales; QIDS-SR: Quick inventory of depressive symptoms–self report; YMRS: Young mania rating scale.

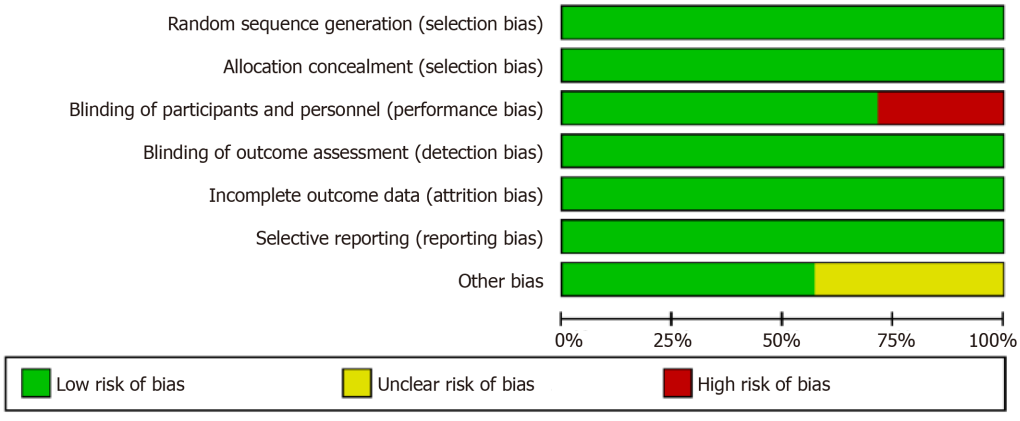


Figure 2 Quality assessments of randomized clinical trials.

on depressive symptoms was near to significant (k = 3, n = 257, g = 1.26, 95%CI: -0.14 to 2.67, P = 0.08, I^2 = 94%).

Subgroup analysis

In order to explore which details of smartphone interventions make them effective for

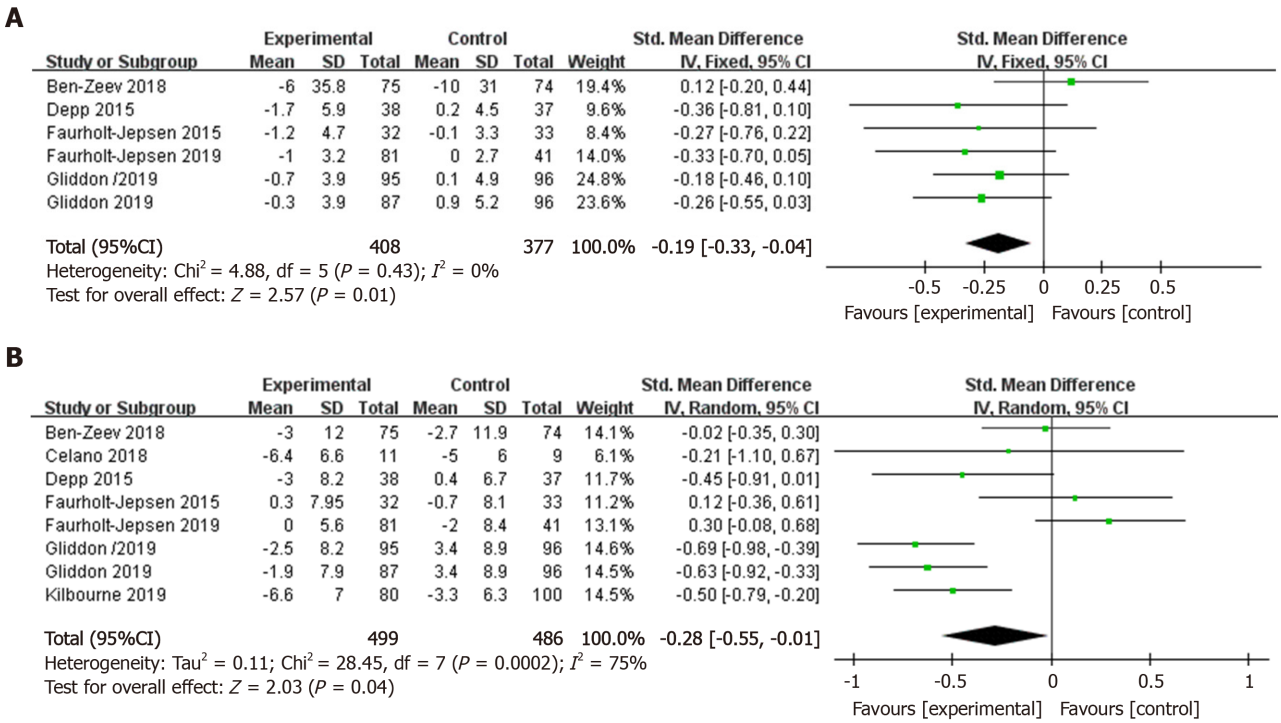


Figure 3 Between-group effect size of smartphone-based interventions on bipolar disorder. A: Meta-analysis of effects of smartphone-based interventions on manic symptoms; B: Meta-analysis of effects of smartphone-based interventions on depressive symptoms.

manic and depressive symptoms, we conducted further subgroup analyses. Smartphone interventions that involved psychoeducation had positive effects on manic symptoms (k = 3, *n* = 449, g = -0.24, 95%CI: -0.43 to -0.06, *P* = 0.01, I^2 = 0) compared to control groups, while those without psychoeducation did not (k = 3, *n* = 336, g = -0.13, 95%CI: -0.43 to 0.17, *P* = 0.39, I^2 = 45%) (Figure 6A). There was no significant subgroup difference (c^2 = 0.36, df = 1, *P* = 0.55) in the effect size obtained for smartphone interventions that involved psychoeducation compared to those without. Our meta-analysis revealed a positive effect size of smartphone mental health interventions for reducing depressive symptoms (k = 3, *n* = 449, g = 0.62, 95%CI: -0.81 to -0.43, *P* < 0.01, I^2 = 0) compared to control groups, while those without psychoeducation were not significantly more efficacious than control conditions in improving depressive symptoms (k = 5, *n* = 536, g = -0.06, 95%CI: -0.39 to 0.26, *P* = 0.71, I^2 =67%) (Figure 6B). There was a significant subgroup difference (c^2 = 8.52, df = 1, *P* = 0.004) in the overall effect size gained for smartphone interventions that involved psychoeducation compared to that did not.

Interventions that involved instruction *via* smartphone had a significantly great effect size on depression outcomes compared to control conditions (k = 2, *n* = 200, g = -0.47, 95%CI: -0.75 to -0.18, *P* = 0.01, I^2 = 0), whereas those without instruction through smartphone did not reduce manic and depressive symptoms compared to control groups (k = 6, *n* = 785, g = -0.24, 95%CI: -0.58 to 0.10, *P* = 0.17, I^2 = 82%) (Figure 7). There was no significant subgroup difference (c^2 = 1, df = 1, *P* = 0.32) in the pooled effect size obtained for interventions that involved instruction *via* smartphone compared to those that did not.

DISCUSSION

As far as we know, this is the first meta-analysis to examine the effects of smartphone-based interventions and monitoring on BD. Ten studies with a total sample of 1028 participants who received smartphone-based treatment or monitoring were used for meta-analysis. The studies were comprehensive in this field. The number of included articles for this meta-analysis was similar to that of a previous meta-analysis that found positive effects from smartphone apps across nine studies with 1837 participants with anxiety[25]. The literature base for BD appears larger than that for other affective disorders, such as post-traumatic stress disorder, according to a recent meta-analysis in this field that included only five relevant articles[27]. Furthermore, six

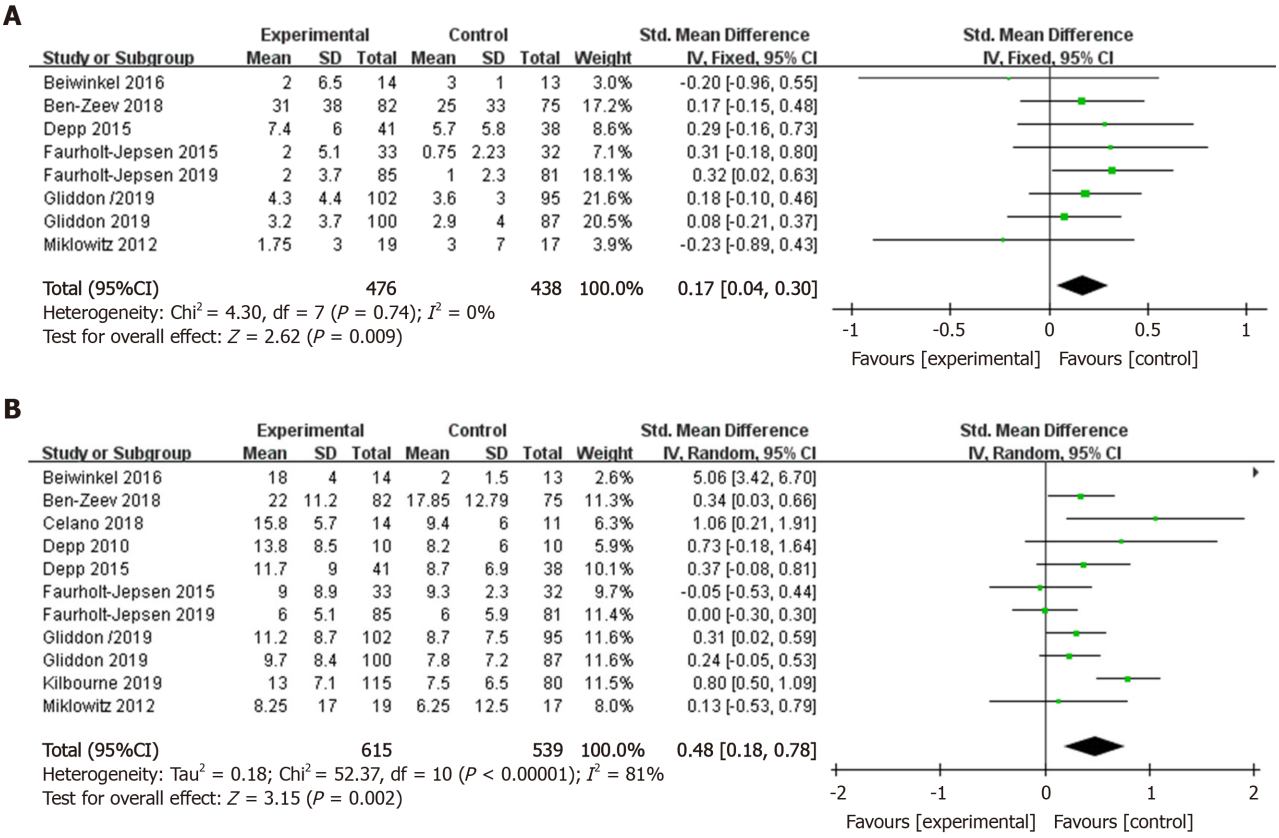


Figure 4 Within-group effect size of smartphone-based interventions on bipolar disorder. A: Meta-analysis of effects of smartphone-based interventions on manic symptoms; B: Meta-analysis of effects of smartphone-based interventions on depressive symptoms.

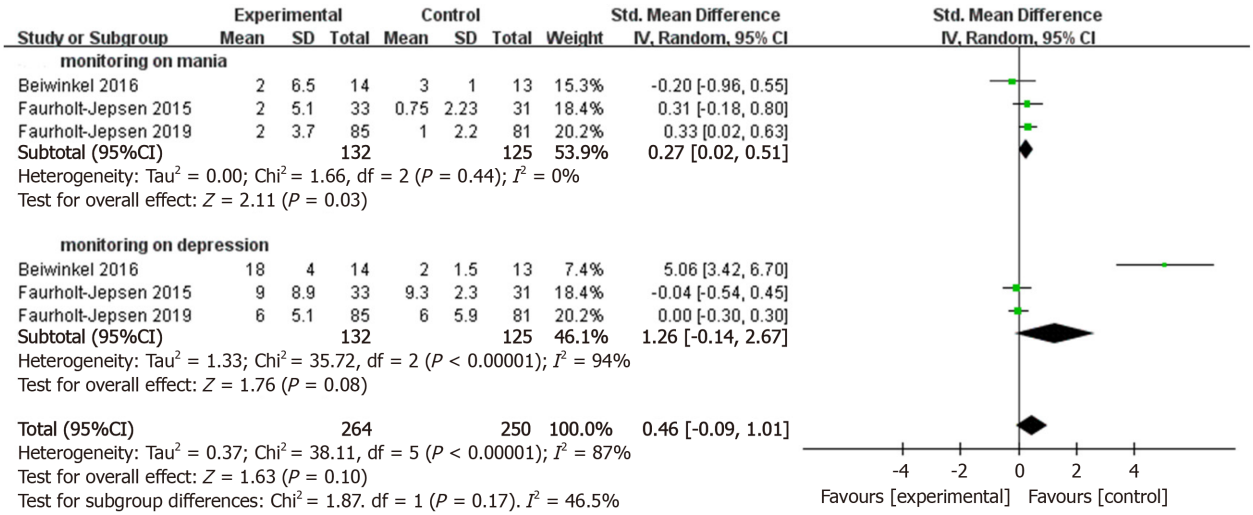


Figure 5 Within-group effect size of smartphone-based monitoring on manic and depressive symptoms.

of our ten articles were published within the past 5 years[14-16,18,21,22], which means that our analysis reflected the effectiveness of the most updated smartphone-based intervention tools.

Our analysis found that smartphone interventions had a positive effect on BD between and within groups. Meta-analysis indicated a positive effect of smartphone-based interventions for reducing manic (g = -0.19) and depressive (g = -0.28) symptoms compared to control groups. In within-group analyses, the effects of smartphone-based interventions appeared effective for manic (g = 0.17) and depressive (g = 0.48) symptoms. Similar positive effects were observed in the meta-analysis of smartphone interventions for other mood disorders, such as anxiety,

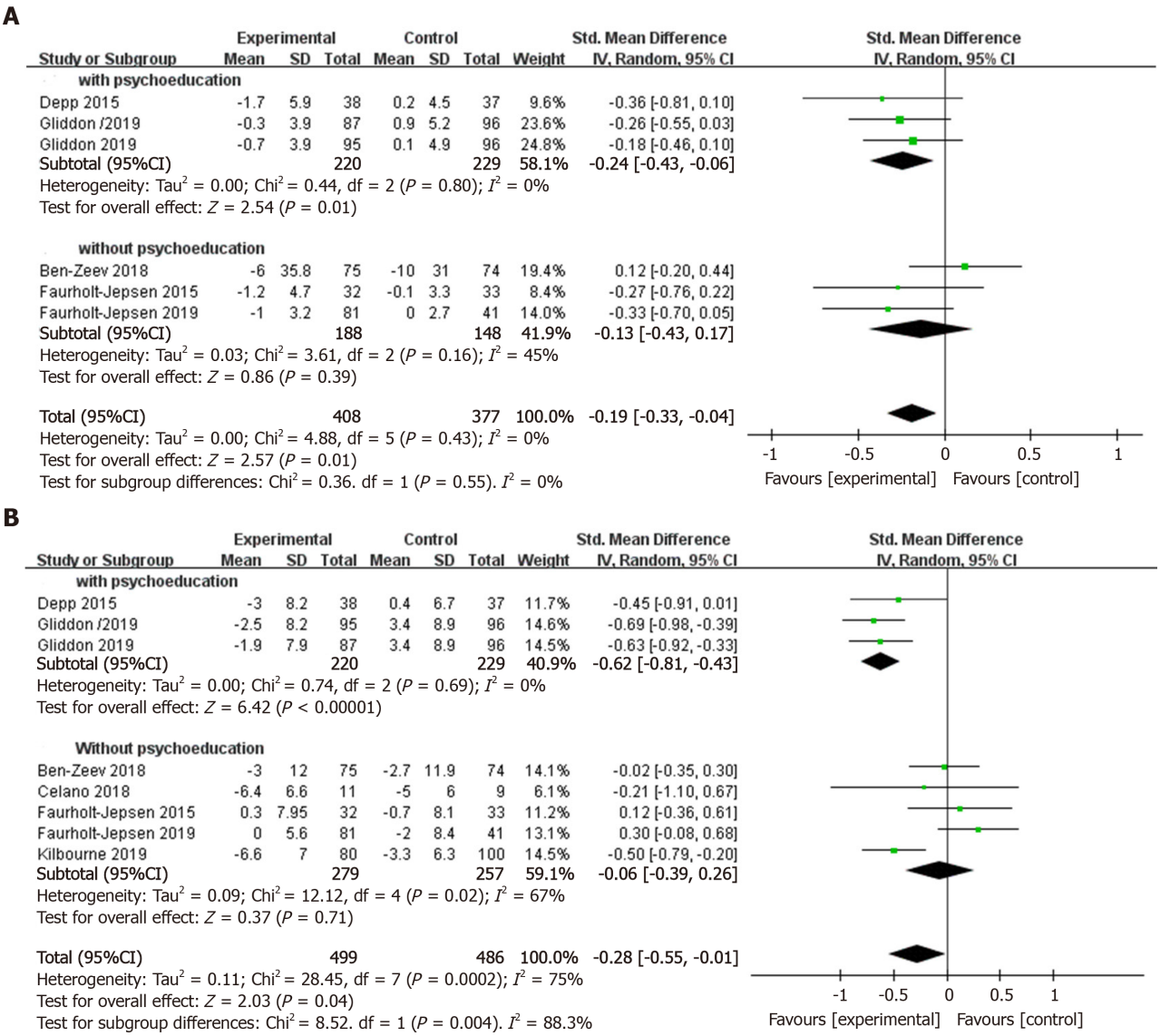


Figure 6 Subgroup analysis of interventions with psychoeducation on bipolar disorder. A: Meta-analysis of effects of smartphone-based interventions on manic symptoms; B: Meta-analysis of effects of smartphone-based interventions on depressive symptoms.

depression, post-traumatic stress disorder, and obsessive compulsive disorder[25-27,37]. These findings indicate that delivering psychological treatments *via* smartphone devices is an efficacious and promising method to treat BD. The potential mechanism by which smartphone interventions reduce symptoms of BD might be explained by using these devices to support and enhance the delivery of existing face-to-face therapy[25]. The use of smartphone-based interventions may provide creative and innovative interventions, filling the gap between feasibility and the demand for treatment[39]. Additionally, interventions *via* smartphone devices may remedy some limitations of existing traditional therapy in the future, with the advantages of convenience and lower treatment cost.

Our analysis showed that BD participants with mania who used the smartphone monitoring systems experienced benefits (g = 0.27). Meanwhile, a recent review of the smartphone application for mood disorders had similar finding that smartphone application with mood monitoring features reduces depressive symptoms[26]. Additionally, a previous study proposed that using a digital device in itself may produce some psychological benefits[40]. The smartphone-based monitoring system was used to collect data on phone usage, social communication, social activity, and mobility, which were irrelevant to psychotherapy. To some extent, using the smartphone-based monitoring system was equivalent to only using the device itself. Therefore, our results that monitoring systems have positive effect on manic symptoms may contribute to the hypothesis that smartphones may offer some psychological benefits. There were three reviews related to the smartphone monitoring

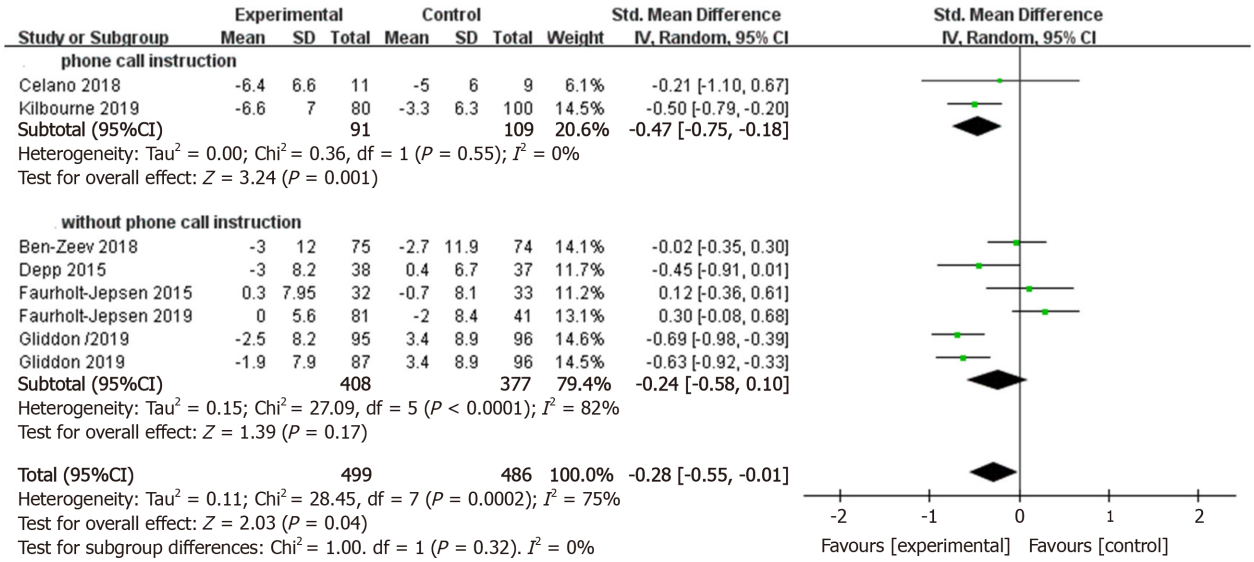


Figure 7 Subgroup analysis of interventions with instruction on depressive symptoms.

system collecting data to predict severity of symptoms[28-30]. Therefore, we conclude that the monitoring system may contribute to treatment of BD and predictions of clinically assessed depressive and manic symptoms. In the future, using smartphone-based monitoring and treatment simultaneously may form a complete treatment system that is convenient and efficient.

With regards to intervention features, in our subgroup analysis, smartphone interventions that involved psychoeducation had great effects on manic (g = -0.24) and depressive (g = -0.62) symptoms of BD compared to control conditions. A similar finding was reported in a recent meta-analysis about psychoeducation for the management of BD patients[41]. The effects of smartphone interventions that involved instruction from the therapist (g = -0.47) appeared significant, while the effect size of those without instruction was not significant. A previous study found that therapist guidance bolstered the effectiveness of smartphone interventions[42]. Instruction from therapists may be conducive to improvement of patient engagement and completion rate of therapy. Although smartphone-based interventions reduced symptoms, there are numerous factors that may affect outcomes of smartphone interventions. Therefore, to design these interventions to be effective in the future, more analyses are needed.

In general, smartphone-based interventions and monitoring reduced symptoms in BD patients. BD is always associated with poor quality of life in addition to personal suffering from depression[43]. Although there are many treatments for BD, there is a limitation in the availability of therapy. The use of smartphones is accessible and affordable[44], which ensures the implementation of mental health interventions and monitoring for BD. It enhances and facilitates the delivery of existing therapy programs and makes them more acceptable. However, there are some complex issues generated by the use of smartphones and the technology itself, including low resource settings somewhere, privacy policy, clinical utility, commercialization, and evolving technology[45-48]. Therefore, in order to achieve satisfactory therapeutic effects in the use of smartphone interventions for BD patients, the influential factors in the whole treatment process should be studied and resolved in the future. Additionally, communication between the users and designers of smartphone-based interventions is not adequate. In the future, the treatment methods will need to be optimized according to the users' feedback and the researchers' thoughts.

Our study had a few limitations. First, two studies in this meta-analysis were considered to have a high risk of bias because of inadequate blinding of participants and personnel[15,18]. Second, the absolute number of available applications is unknown and the applications are frequently updated. It is impossible to examine total smartphone interventions. Third, there were only three eligible articles regarding smartphone-based monitoring patterns[14,18,19], which was not sufficient to provide definitive results. Future research that directly tests the monitoring effectiveness against BD would add value to our results. Lastly, to explore potential factors relevant to smartphone interventions, details about demographics, severity of BD, and

engagement need to be collected. Nevertheless, with limited data that can be extracted, we could not conduct subgroup analysis on these variables that might impact statistical results. In the future, a more standard data reporting format needs to be implemented with research data, thus improving the validity and reliability of meta-analysis.

CONCLUSION

In summary, smartphone-based interventions are effective in reducing manic and depressive symptoms. Nevertheless, the smartphone-based monitoring systems only worked for participants with manic but not depressive symptoms. Our results contribute to the literature on smartphone-based interventions and monitoring for manic and depressive symptoms in BD patients, although much work remains to be done. This meta-analysis shows that smartphone-based intervention and monitoring have the potential to enhance the methods of treatment with its characteristics of low expenditure and highly-convenience in addition to available medications and psychological interventions.

ARTICLE HIGHLIGHTS

Research background

Recently, a range of studies about smartphone-based interventions and monitoring for reducing symptoms of bipolar disorder (BD) have been published. However, their efficacy for BD remains unclear.

Research motivation

The present study aimed to assess randomized controlled trials and single-group trials of smartphone-based interventions and monitoring for reducing the symptoms of BD.

Research objectives

The main objective was to update and evaluate innovative treatment suggestions for BD.

Research methods

We performed a systematic literature search on PubMed, Embase, Clinical trials, psycINFO, Web of Science, and Cochrane Library. Randomized clinical trials or single-group trials in which smartphone-based interventions and monitoring were compared with control methods or baseline in patients with symptoms of BD were included. We synthesized data using a random-effects or a fixed-effects model by Review Manager version 5.3 to analyze the effects of psychological interventions and monitoring delivered *via* smartphone on psychiatric symptoms in patients with BD. The primary outcome measures were set for mania and depression symptoms. The subgroups were created to explore which aspects of smartphone interventions are relevant to the greater or lesser efficacy of treating symptoms.

Research results

We identified ten articles, including seven randomized clinical trials (985 participants) and three single-group trials (169 participants). Analysis of the between-group study showed that smartphone-based interventions had positive effects in reducing manic (g = -0.19, 95%CI: -0.33 to -0.04, $P = 0.01$) and depressive (g = -0.28, 95%CI: -0.55 to -0.01, $P < 0.05$) symptoms. In within-group analysis, smartphone-based interventions significantly reduced manic (g = 0.17, 95%CI: 0.04 to 0.30, $P < 0.01$) and depressive (g = 0.48, 95%CI: 0.18 to 0.78) symptoms compared to the baseline. Nevertheless, smartphone-based monitoring systems significantly reduced manic (g = 0.27, 95%CI: 0.02 to 0.51, $P < 0.05$) but not depressive symptoms. Subgroup analysis indicated that the interventions with psychoeducation were effective for depressive (g = -0.62, 95%CI: -0.81 to -0.43, P < 0.01) and manic (g = -0.24, 95%CI: -0.43 to -0.06, $P = 0.01$) symptoms compared to the controlled conditions, while the interventions without psychoeducation did not ($P > 0.05$). The contacts between therapists and patients that contributed to the implementation of psychological therapy reduced depression symptoms (g = -0.47, 95%CI: -0.75 to -0.18, $P = 0.01$).

Research conclusions

Smartphone-based interventions and monitoring have a significant positive impact on depressive and manic symptoms of BD patients in between-group and within-group analysis.

Research perspectives

The current meta-analysis suggests that smartphone-based interventions provide evidence of any reduction in manic and depressive symptoms. Nevertheless, smartphone-based monitoring systems are only effective for participants with manic but not depressive symptoms. The findings have implied that these digital tools can be used as the clinically future treatments for symptoms of BD. However, future trials need to keep pace with the development of these apps and a better understanding of the numerous factors that influence outcomes of smartphone interventions for BD are also required.

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ORIGINAL ARTICLE

Basic Study

Identification of key genes involved in post-traumatic stress disorder: Evidence from bioinformatics analysis

Yao-Yao Bian, Li-Li Yang, Bin Zhang, Wen Li, Zheng-Jun Li, Wen-Lin Li, Li Zeng

ORCID number: Yao-Yao Bian 0000-0002-9968-2501; Li-Li Yang 0000-0001-5220-3094; Bin Zhang 0000-0002-2339-6349; Wen Li 0000-0002-3975-3312; Zheng-Jun Li 0000-0001-8208-3898; Wen-Lin Li 0000-0002-7105-2743; Li Zeng 0000-0002-9095-9439.

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Yao-Yao Bian, School of Nursing, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu Province, China

Li-Li Yang, Li Zeng, School of First Clinical Medicine, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu Province, China

Li-Li Yang, Wen-Lin Li, Li Zeng, Jingwen Library, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu Province, China

Bin Zhang, Digestive Department, Ningbo Hospital of Traditional Chinese Medicine, Ningbo 315200, Zhejiang Province, China

Wen Li, School of Preclinical Medicine, Guizhou University of Traditional Chinese Medicine, Guiyang 550025, Guizhou Province, China

Zheng-Jun Li, Management School, University of St Andrews, St Andrews KY16 9AJ, United Kingdom

Zheng-Jun Li, College of Health Economics Management, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu Province, China

Corresponding author: Li Zeng, MD, PhD, Academic Research, School of First Clinical Medicine, Nanjing University of Chinese Medicine, No. 138 Xianlin Avenue, Qixia District, Nanjing 210023, Jiangsu Province, China. zengbingli@njucm.edu.cn

Abstract

BACKGROUND

Post-traumatic stress disorder (PTSD) is a serious stress-related disorder.

AIM

To identify the key genes and pathways to uncover the potential mechanisms of PTSD using bioinformatics methods.

METHODS

Gene expression profiles were obtained from the Gene Expression Omnibus database. The differentially expressed genes (DEGs) were identified by using GEO2R. Gene functional annotation and pathway enrichment were then conducted. The gene-pathway network was constructed with Cytoscape software. Quantitative real-time polymerase chain reaction (qRT-PCR) analysis was applied

for validation, and text mining by Coremine Medical was used to confirm the connections among genes and pathways.

RESULTS

We identified 973 DEGs including 358 upregulated genes and 615 downregulated genes in PTSD. A group of centrality hub genes and significantly enriched pathways (MAPK, Ras, and ErbB signaling pathways) were identified by using gene functional assignment and enrichment analyses. Six genes (*KRAS*, *EGFR*, *NFKB1*, *FGF12*, *PRKCA*, and *RAF1*) were selected to validate using qRT-PCR. The results of text mining further confirmed the correlation among hub genes and the enriched pathways. It indicated that these altered genes displayed functional roles in PTSD *via* these pathways, which might serve as key signatures in the pathogenesis of PTSD.

CONCLUSION

The current study identified a panel of candidate genes and important pathways, which might help us deepen our understanding of the underlying mechanism of PTSD at the molecular level. However, further studies are warranted to discover the critical regulatory mechanism of these genes *via* relevant pathways in PTSD.

Key Words: Post-traumatic stress disorder; Differentially expressed genes; Key pathway; Gene-pathway co-expression; Bioinformatics analysis; Microarray

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Core Tip: Post-traumatic stress disorder (PTSD) is an affective disorder after exposure to trauma or stress directly or indirectly. The pathogenesis of PTSD is not entirely understood. The purpose of this study was to uncover the critical signatures and key pathways to elucidate the underlying mechanisms of PTSD at the molecular level. To address this issue, the closely related genes and the most enriched pathways were identified by using bioinformatics analysis, which was then validated by using basic study in an exploratory approach. Our results showed that a series of significantly expressed genes and relevant pathways might serve as potential biomarkers involved in the pathogenesis of PTSD.

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INTRODUCTION

Post-traumatic stress disorder (PTSD), a serious stress-related disorder, is characterized as hypervigilance or hyperarousal, which is caused by traumatic exposure or stressful event directly or indirectly[1]. It presents with a wide range of significant symptoms, *e.g.*, disturbing when reminding the flashbacks, avoidance following re-experiencing the traumatic events, and negative changes in mood and cognitive[2]. It is diagnosed when these symptoms last for at least 1 mo after traumatic or stressor-related exposure[3].

It is estimated that the prevalence of PTSD ranges from 3.1% to 61.6% among 6648 participants in six countries by the International Consortium to Predict PTSD project[4]. In a recent meta-analysis of 96 studies representing 34 countries, a 15.3% prevalence rate of PTSD was found[5]. The lifetime rate of PTSD in the United States population is about 6.8%[6]. A recent cross-sectional study performed in France showed that 35.3% of adults were diagnosed with PTSD[7]. Additionally, about 89.7% of United States adults have exposed at least one traumatic event[8]. Even though PTSD afflicts millions of people throughout the world, it remains largely undiagnosed, particularly in developing countries like China. It is not only comorbid with a wide range of

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psychological disorders (*i.e.*, depression, anxiety, and substance abuse), which may further cause suicidal ideation or aggressive/addictive behaviors, but also associated with multiple negative psychosocial outcomes such as marital difficulties and unemployment. PTSD has brought a significant burden on individuals, families, and countries. It is reported that the United States spent more than 45 billion dollars annually on the treatment of mental disorders like PTSD[9]. At present, the understanding of the underlying mechanisms of PTSD is not entirely clear, but it is likely related to the hypothalamic-pituitary-adrenal axis, neural circuits, autonomic nervous system, as well as the immune system. Taken together, these facts highlight an urgent need to uncover the molecular mechanisms of PTSD.

To date, with the advances of genomic and transcriptomic study, increasing genes and pathways have been screened out and reported to be related to the occurrence and development of PTSD. For instance, previous studies[10,11] showed that FK506 binding protein 51 was associated with PTSD by deregulating the hypothalamic-pituitary-adrenal axis, indicating a key modulator of PTSD risk. In another instance, a gene-based study[12] found that beta 2 adrenergic receptor gene was related to childhood trauma exposure in predicting PTSD symptoms in adults. Additionally, a variety of signaling pathways were reported to be involved in the developmental progression of PTSD, *i.e.*, NF-κB pathway[13], BDNF-TrkB pathway[14], and JAK/STAT pathway[15], *etc.* Hence, it is necessary to identify candidate genes and relevant pathways involved in the onset and development of PTSD.

In this study, we screened out a group of candidate signatures and key pathways associated with PTSD from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database by using bioinformatics analysis. Furthermore, the results were verified by using the experimental methods. Our results may provide a significant step forward in understanding the pathogenesis of PTSD at the molecular level.

MATERIALS AND METHODS

Data resources and data processing

The gene expression profile of GSE68077 submitted by Muhie *et al*[16] was obtained for our analysis. In this study, the microarray data of hemibrain samples were collected for analysis. GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r) is an online tool based on the GEO query and Limma R packages. It was conducted to screen differentially expressed genes (DEGs) from different groups of different GEO series[17]. The significant DEGs were obtained by meeting both $|\log FC| > 1$ and $P < 0.05$. The Venny online tool (available online: http://bioinfogp.cnb.csic.es/tools/venny) was used to identify overlapping DEGs across two groups. The common genes were preserved for further bioinformatics analysis.

Functional enrichment analysis

Gene ontology (GO) enrichment analysis was used for gene annotation and function description. It consisted of three regulated functions, that is, biological processes (BP), cellular component (CC), and molecular function (MF). The GO terms were identified using the Database for Annotation, Visualization, and Integrated Discovery (DAVID, available online: http://david.abcc.ncifcrf.gov/)[18] to identify the biological significance of genes when $P < 0.05$ was considered statistically significant. The Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis was conducted using DAVID[18] to identify pathway enrichment when $P < 0.05$ was set as the threshold value.

Gene–pathway network construction and prediction

The identified genes and significantly enriched pathways mapped with Cytoscape (http://www.cytoscape.org) software[19] was used to visualize the integrated regulatory networks. Text mining conducted by Coremine Medical (http://www.coremine.com/medical/)[20] was used to visualize the connections among genes and pathways.

Experimental animals and model preparation

Six male SJL albino mice (weighing 30 ± 2 g) provided by the Beijing Vital River Laboratory Animal Technology Co., Ltd (Beijing, China) were trained as aggressor mice according to the study[21]. The mice were housed in home cages that were made of

plexiglass material with plenty of water and food. Twelve male C57BL/6N mice (weighing 18 ± 2 g) were purchased from Changzhou Cavens Laboratory Animal Co., Ltd (Changzhou, China). They were randomly assigned to a control or an aggressed-exposed (Agg-E) group. All mice were housed under a standard condition on a 12-h light/darkness cycle in a temperature-controlled room (23 ± 2 ℃). As described previously[22], we used a modified "cage-within-cage resident-intruder" protocol[23] to prepare the social stressed models. Briefly, Agg-E mice were housed in a wire mesh cage (17 cm × 14 cm × 8 cm), which were put inside the aggressor's larger home cage (50 cm × 30 cm × 20 cm) for 6 h per day. The control mice were treated without aggressor exposure in the same condition. During the exposure time, the experimental mice were given no water and food, while the aggressor mice had free access to them. The direct or indirect exposure lasted for 10 successive days. After 6 wk of recovery, all experimental mice were sacrificed to harvest hemibrain tissues.

Depression-like behavior tests

All mice underwent three depression-like behavior tests, that is, forced swim test (FST), tail suspension test (TST), and open-field test (OFT). These tests were described previously[23,24]. In brief, the mice were put in a transparent, glass cylindrical tank (2500 mL total volume) filled with 20 cm water (25 ± 1℃) and swam for 6 min. The time when they remained floating passively, stopped struggle, or swimming was regarded as the immobility time. The last 4 min of the immobility time was recorded with a video camera in the FST test. For TST, the mice were suspended by the tail and the last 4 min of the immobility time were measured. While the OFT test was conducted to assess locomotor activity. The mice were allowed to move freely in a specific device for 5 min. The movements of each mouse were measured with a video camera.

Quantitative real-time polymerase chain reaction (qRT-PCR) analysis

Total RNA of hemibrain tissues was isolated according to the instructions of the kit. Polymerase chain reaction was conducted using the SYBR Green Master Mix (ThermoFisher, United States). The gene expression was calculated by $2^{-\Delta\Delta CT}$ method and normalized against the reference gene, *GAPDH*. The primers are presented in Supplementary Table 1.

Data analysis and statistics

The experimental results are all shown as the mean ± SD. Intergroup differences were analyzed by the *t*-test by using the SPSS 19.0 software. A *P* value less than 0.05 was regarded as statistically significant.

RESULTS

Identification of DEGs

First, we retrieved DEGs at two-time points (24 h post 10 d and 42 d post 10 d) by using GEO2R, separately. A total of 1432 DEGs (577 upregulated DEGs and 855 downregulated DEGs) at the time point of 24 h post 10 d, and 1374 DEGs (569 upregulated DEGs and 805 downregulated DEGs) at the time point of 42 d post 10 d were obtained. Based on Venny online tool, a total of 358 overlapping upregulated DEGs and 615 overlapping downregulated DEGs of the two-time points were identified in the social-stress group compared with the control group. The Venny diagram of upregulated and downregulated DEGs was shown in Figure 1.

Functional annotations

The 973 DEGs (358 upregulated DEGs and 615 downregulated DEGs) were assessed using the DAVID database for functional assignment and pathway enrichment with a *P* value < 0.05. We identified the most enriched GOs (top 20) ranked by *P* value, including protein binding (GO: 0005515), cell junction (GO: 0030054), and neuron projection (GO: 0043005) (Figure 2A). Functional enrichment analysis based on GO terms showed that these altered genes significantly participated in PTSD-related pathways (top 20, Figure 2B), *i.e.*, MAPK, Ras, and ErbB signaling pathways.

The above 358 upregulated DEGs and 615 downregulated DEGs were analyzed using DAVID, respectively. Based on *P* value, the upregulated genes in BP terms were markedly enriched in nervous system development, cell differentiation, and positive regulation of neuron projection development. The upregulated genes in CC terms were mainly associated with cell junction, and the upregulated genes in MF terms

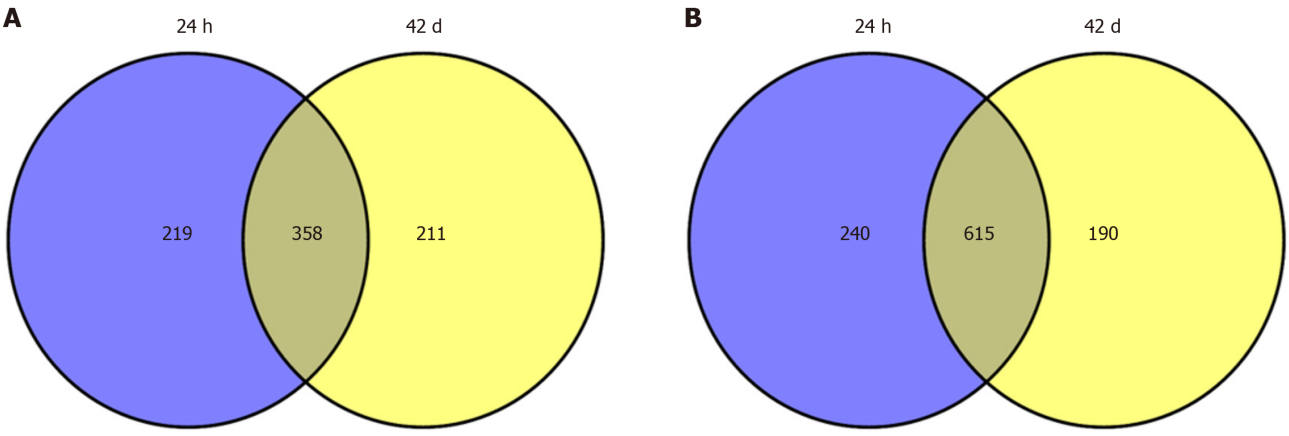


Figure 1 Venny diagrams of differentially expressed genes at the time point of 24 h post 10 d compared with 42 d post 10 d after aggressor exposure sessions. A: Overlapping upregulated differentially expressed genes; B: Overlapping downregulated differentially expressed genes.

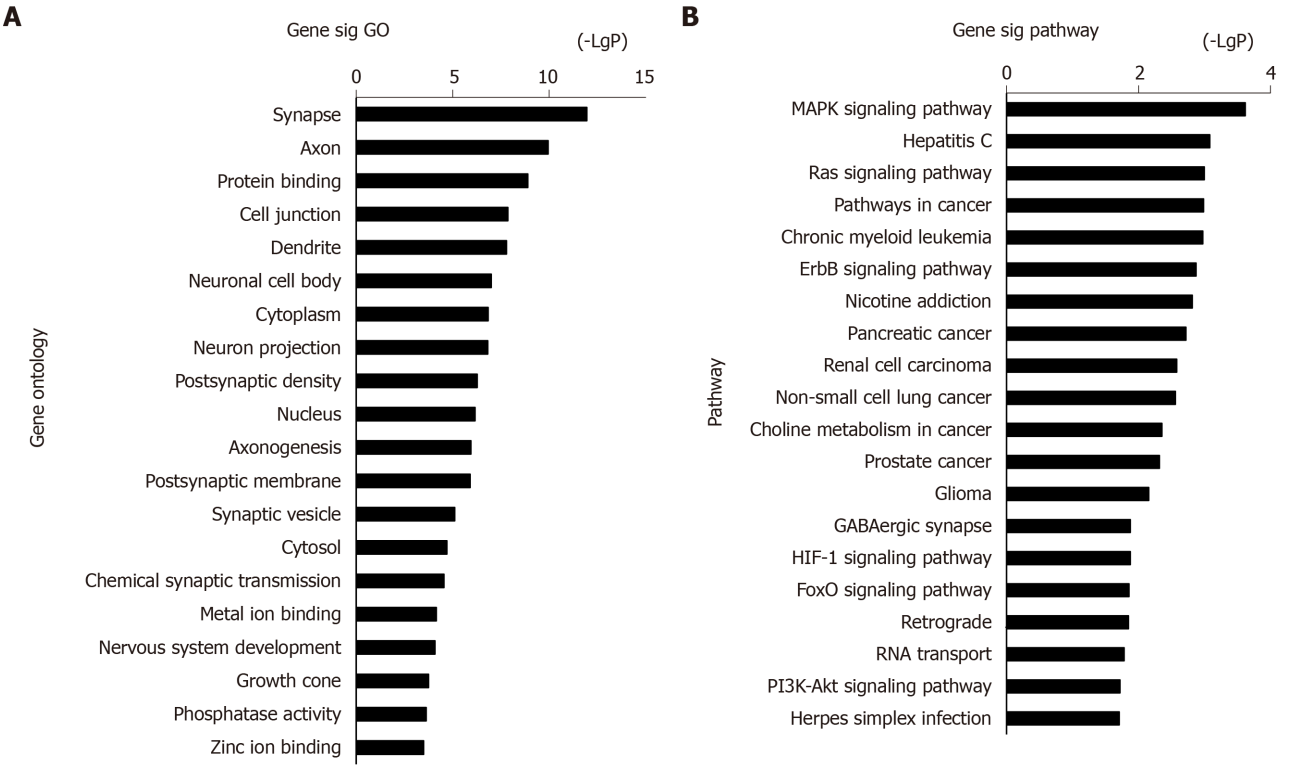


Figure 2 Gene ontology annotation and pathway enrichment of differentially expressed genes associated with post-traumatic stress disorder. A: Gene ontology analysis of differentially expressed genes (top 20); B: The Kyoto Encyclopedia of Genes and Genomes enrichment analysis of differentially expressed genes (top 20) with enriched score values setting as –log10 (*P* values). GO: Gene ontology.

were markedly enriched in cell adhesion molecule binding and protein domain specific binding. Meanwhile, the downregulated genes in BP terms were markedly enriched in protein transport, cell cycle, and vesicle-mediated transport. The downregulated genes in MF terms were markedly enriched in protein binding, nucleic acid binding, and nucleocytoplasmic transporter activity (Table 1). Furthermore, KEGG enrichment analysis results showed that the upregulated genes were enriched in neuroactive ligand-receptor interaction, calcium signaling pathway, and MAPK signaling pathway, while the downregulated genes were enriched in the ErbB signaling pathway and Toll-like receptor signaling pathway (Table 2). Combined with the results in Figure 2, MAPK, Ras, and ErbB signaling pathways were the main PTSD-related pathways. These markedly enriched pathways with their DEGs are presented in Table 3. Finally, these genetic pathways with their genes were uploaded to Cytoscape to construct the co-expression pattern of the most significantly enriched

Table 1 Gene ontology annotations of differentially expressed genes associated with post-traumatic stress disorder (top 5)

Expression	Category	Term	Function	Count	*P* value
Up-regulated	BP	GO: 0007399	Nervous system development	25	1.21E–08
	BP	GO: 0007409	Axonogenesis	14	1.82E–08
	BP	GO: 0007268	Chemical synaptic transmission	16	1.33E–07
	BP	GO: 0030154	Cell differentiation	32	3.75E–06
	BP	GO: 0010976	Positive regulation of neuron projection development	12	1.51E–05
	CC	GO: 0045202	Synapse	43	1.25E–18
	CC	GO: 0043025	Neuronal cell body	39	1.18E–14
	CC	GO: 0030425	Dendrite	37	2.35E–14
	CC	GO: 0030054	Cell junction	44	7.70E–14
	CC	GO: 0030424	Axon	31	3.10E–13
	MF	GO: 0005515	Protein binding	99	3.15E–05
	MF	GO: 0050839	Cell adhesion molecule binding	8	1.71E–04
	MF	GO: 0019904	Protein domain specific binding	15	3.48E–04
	MF	GO: 0005216	Ion channel activity	11	5.51E–04
	MF	GO: 0008144	Drug binding	8	0.002625
Down-regulated	BP	GO: 0015031	Protein transport	38	7.01E–06
	BP	GO: 0007049	Cell cycle	38	1.59E–05
	BP	GO: 0016192	Vesicle-mediated transport	17	4.14E–04
	BP	GO: 0007040	Lysosome organization	7	7.61E–04
	BP	GO: 0006281	DNA repair	21	8.39E–04
	CC	GO: 0005737	Cytoplasm	243	1.19E–08
	CC	GO: 0005634	Nucleus	219	2.55E–07
	CC	GO: 0005829	Cytosol	77	5.42E–05
	CC	GO: 0005768	Endosome	30	4.60E–04
	CC	GO: 0005794	Golgi apparatus	53	4.91E–04
	MF	GO: 0046872	Metal ion binding	135	4.24E–06
	MF	GO: 0005515	Protein binding	156	1.17E–05
	MF	GO: 0003676	Nucleic acid binding	61	1.93E–05
	MF	GO: 0005487	Nucleocytoplasmic transporter activity	5	0.001069
	MF	GO: 0016874	Ligase activity	22	0.001335

BP: Biological processes; CC: Cellular component; MF: Molecular function; GO: Gene ontology.

pathways of DEGs involved in PTSD, as shown in Figure 3.

Verification and text mining of hub genes and pathways

The genes in the central roles connected to the three enriched pathways were considered as hub genes. In our study, we tried to uncover the closely enriched genes related to the most significant pathways in an exploratory approach. Six hub genes were selected based on the literature due to their neurobiology assumption to be related to PTSD. The hub genes were listed as follows, that is, nuclear factor kappa B subunit 1 (*NFKB1*), KRAS proto-oncogene, GTPase (*KRAS*), epidermal growth factor receptor (*EGFR*), fibroblast growth factor 12 (*FGF12*), protein kinase C alpha (*PRKCA*), and Raf-1 proto-oncogene, serine/threonine kinase (*RAF1*). qRT-PCR was used for validation. The above genes in hemibrain tissues were differently expressed between the two groups (Figure 4), which was in line with the results of the microarray

Table 2 Kyoto Encyclopedia of Genes and Genomes analysis of differentially expressed genes associated with post-traumatic stress disorder (top 10)

Expression	Term	Definition	Count	*P* value
Upregulated	mmu04080	Neuroactive ligand-receptor interaction	16	2.02E–05
	mmu05014	ALS	6	1.08E–04
	mmu04530	Tight junction	8	1.23E–03
	mmu00430	Taurine and hypotaurine metabolism	2	1.30E–03
	mmu04020	Calcium signaling pathway	9	2.08E–03
	mmu00650	Butanoate metabolism	3	3.77E–03
	mmu04512	ECM-receptor interaction	5	6.91E–03
	mmu05322	Systemic lupus erythematosus	7	8.98E–03
	mmu04720	Long-term potentiation	4	1.25E–02
	mmu04010	MAPK signaling pathway	10	1.31E–02
Downregulated	mmu05223	Non-small cell lung cancer	9	1.48E–05
	mmu05212	Pancreatic cancer	10	2.35E–05
	mmu05160	Hepatitis C	14	4.31E–05
	mmu05211	Renal cell carcinoma	8	6.64E–04
	mmu05221	Acute myeloid leukemia	7	6.55E–04
	mmu04012	ErbB signaling pathway	9	6.19E–04
	mmu04620	Toll-like receptor signaling pathway	10	5.05E–04
	mmu03013	RNA transport	14	3.89E–04
	mmu05214	Glioma	8	3.55E–04
	mmu05215	Prostate cancer	10	1.91E–04

ALS: Amyotrophic lateral sclerosis; ECM: Extracellular matrix.

Table 3 The most significantly enriched pathways of differentially expressed genes associated with post-traumatic stress disorder

Term	Pathway	*P* value	Genes	
			Upregulated	Downregulated
mmu04010	MAPK signaling pathway	1.51E–08	*Crkl, Fgf12, Mras, Mapt, Ntrk2, Dusp8, Ptpn5, Map3k4, Mapk8ip2, Dusp7*	*Chuk, Egf, Egfr, Ikbkg, Kras, Nfkb1, Prkca, Pla2g4a, Sos1, Map3k8, Stk3, Tab2, Dusp16, Raf1, Taok1*
mmu04014	Ras signaling pathway	1.84E–07	*Fgf12, Grin2b, Mras, Pgf, Ptpn11, Gng13*	*Chuk, Egf, Egfr, Gab1, Ikbkg, Insr, Kras, Nfkb1, Pik3ca, Prkca, Pla2g4a, Sos1, Rassf5, Tbk1, Raf1, Rab5a*
mmu04012	ErbB signaling pathway	3.85E–06	*Camk2b, Cdkn1b, Crkl*	*Egf, Egfr, Gab1, Kras, Pik3ca, Prkca, Sos1, Tgfa, Raf1*

datasets. It indicated that these genes played crucial roles in the occurrence and development of PTSD. To further visualize the linear connections between the hub genes and the associated pathways, text mining was performed with Coremine Medical online tool. The above six gene symbols and three pathways were used as search terms, and the co-expressed network is shown in Figure 5. We found that *KRAS* and *EGFR* were correlated with the Ras pathway, while four genes (*KRAS*, *EGFR*, *PRKCA*, and *RAF1*) were related to the ErbB pathway. The genes except *FGF12* were associated with the MAPK pathway. More importantly, *EGFR* and *KRAS* were connected with three pathways, which further demonstrated that these genes have important biological functions in the signaling pathway.

Depression-like behavior analysis

The results of FST, TST, and OFT are presented in Figure 6. We found that the

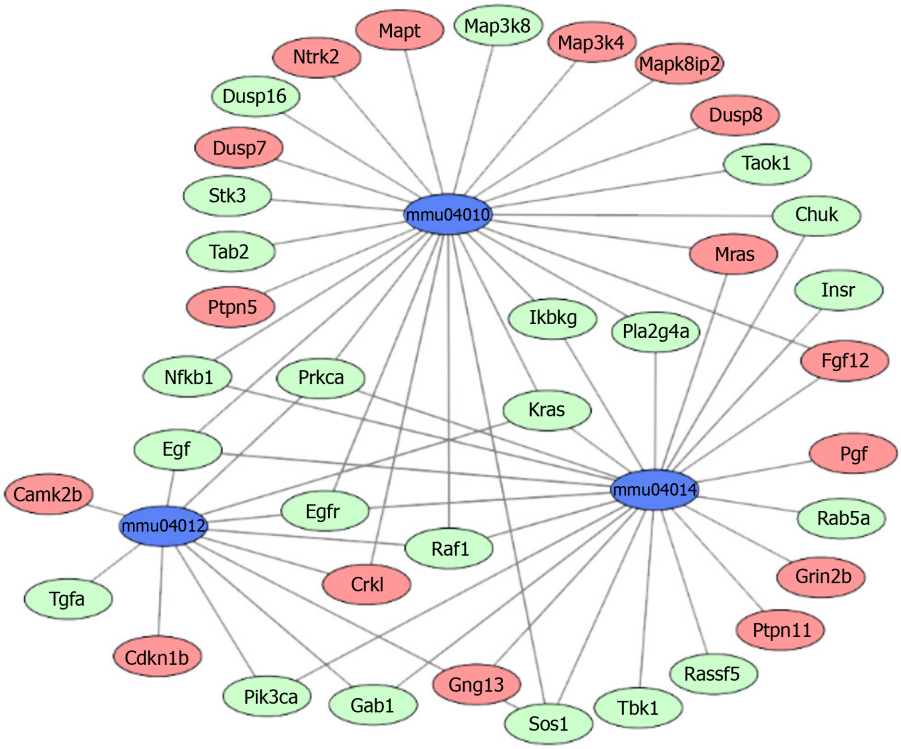


Figure 3 Co-expression pattern of the most significantly enriched pathways of differentially expressed genes involved in post-traumatic stress disorder. In the graphic, red cycles as the upregulated genes, green cycles as the downregulated genes, and blue cycles as the signaling pathway.

immobility time in the Agg-E group was significantly increased than that of the control group. However, the path length of OFT showed no significant difference between the Agg-E group and control group.

DISCUSSION

PTSD as a trauma-related or stressor-related disorder is the consequence of direct or indirect stress. It can lead to subsequent response patterns such as avoidance, negative emotion, and hyperarousal[2]. PTSD is diagnosed when the above symptoms last for at least 1 mo after the onset of the event[25]. The genesis and progression of PTSD are complicated and the pathogenesis is not entirely understood. Thus, it is needed to uncover the key targets to elucidate the underlying mechanisms associated with PTSD.

In this study, the gene expression microarrays of GSE68077 were downloaded from the GEO database. A total of 973 DEGs including 358 upregulated genes and 615 downregulated genes were identified. The functional enrichment analysis of DEGs based on GO terms demonstrated that the most functional and molecular work might focus on MAPK, Ras, and ErbB signaling pathways. Based on functional enrichment, we found that the upregulated genes displayed functionalities, such as cell differentiation and positive regulation of neuron projection development, while the downregulated genes had other functionalities, such as protein transport, cell cycle, and DNA repair. The upregulated genes were markedly concentrated in neuroactive ligand-receptor interaction, calcium, and MAPK signaling pathways, and the downregulated genes were markedly enriched in the ErbB and Toll-like receptor signaling pathways. Taken together, we speculated that MAPK, Ras, and ErbB pathways played regulatory roles in the occurrence and progression of PTSD. Consistent with our hypothesis, the MAPK pathway as a kind of stress response signaling cascade, is involved in synaptic plasticity and is connected with depressive-like symptoms or severity of the depression[26]. In line with our findings, a previous study[27] based on bioinformatics analysis showed that the MARK signaling pathway was one of the mainly enriched signaling pathways involved in major depressive disorder. Another study suggested that the ErbB signaling pathway might be associated with cognitive deficiencies after early social isolation[28], and Ras pathway acted as a critical role in the pathogenesis of depression[29].

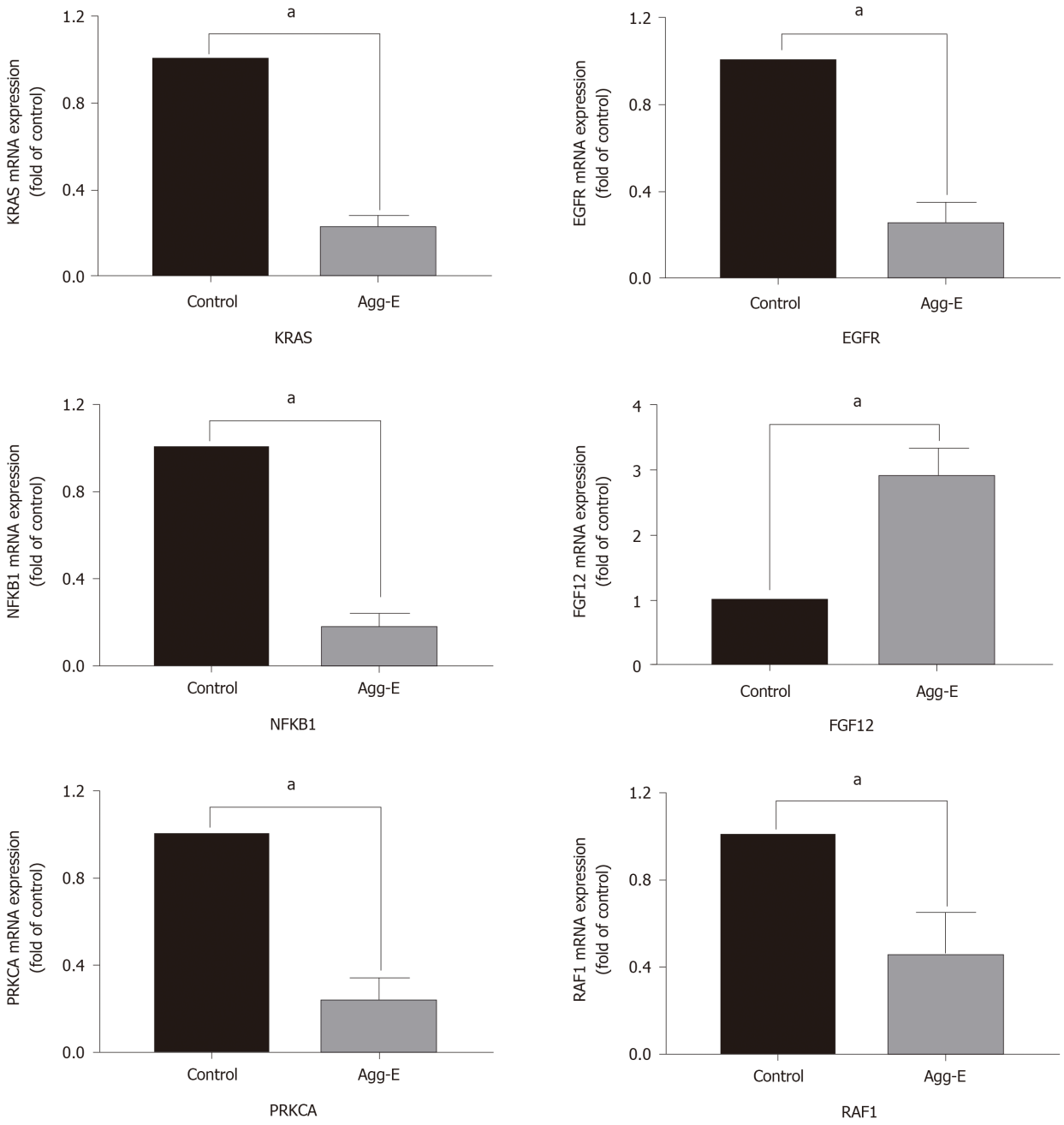


Figure 4 The mRNA expression of hub genes in control and aggressed-exposed groups. The results are shown as the mean ± SD, $^{a}P < 0.05$. Agg-E: Aggressed-exposed; *KRAS*: *KRAS* proto-oncogene, GTPase; *EGFR*: Epidermal growth factor receptor; *NFKB1*: Nuclear factor kappa B subunit 1; *FGF12*: Fibroblast growth factor 12; *PRKCA*: Protein kinase C alpha; *RAF1:* Raf-1 proto-oncogene, serine/threonine kinase.

Currently, we identified the closely related genes involved in the most significant pathways above, as shown in Table 3. Among these genes, we found that a panel of hub genes was closely related to the significantly expressed pathways. In an exploratory approach, several hub genes were selected based on the literature due to their neurobiology assumption to be related to PTSD. To validate our hypothesis, we further performed qRT-PCR to verify our findings. The results were consistent with the microarray analysis. Besides, several genes were reported in previous studies. For example, NFKB1, a transcription regulator, was found to be overexpressed in depressive disorders patients[30]. PRKCA has been implicated in PTSD pathogenesis, and the single nucleotide polymorphism of *PRKCA* was considered to be significantly associated with traumatic experiences and PTSD symptoms, which can further increase the rate of PTSD[31]. EGFR plays a vital role in cellular growth, differentiation, and apoptosis. Several studies indicated that EGFR genotype is closely correlated to depression or major depressive disorder[32-34]. Its main downstream pathway is MAPK that plays a dominant role in signal transduction in many biological activities such as

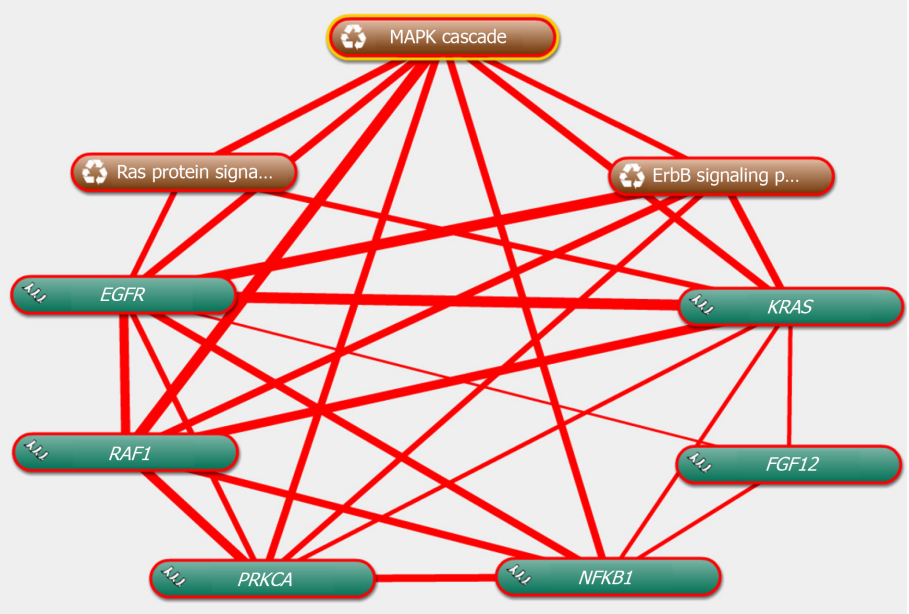


Figure 5 Linear association among the hub genes and co-expressed pathways using Coremine Medical online tool. The thicker the line, the closer the relationship. *KRAS*: KRAS proto-oncogene, GTPase; *EGFR*: Epidermal growth factor receptor; *NFKB1*: Nuclear factor kappa B subunit 1; *FGF12*: Fibroblast growth factor 12; *PRKCA*: Protein kinase C alpha; *RAF1*: Raf-1 proto-oncogene, serine/threonine kinase.

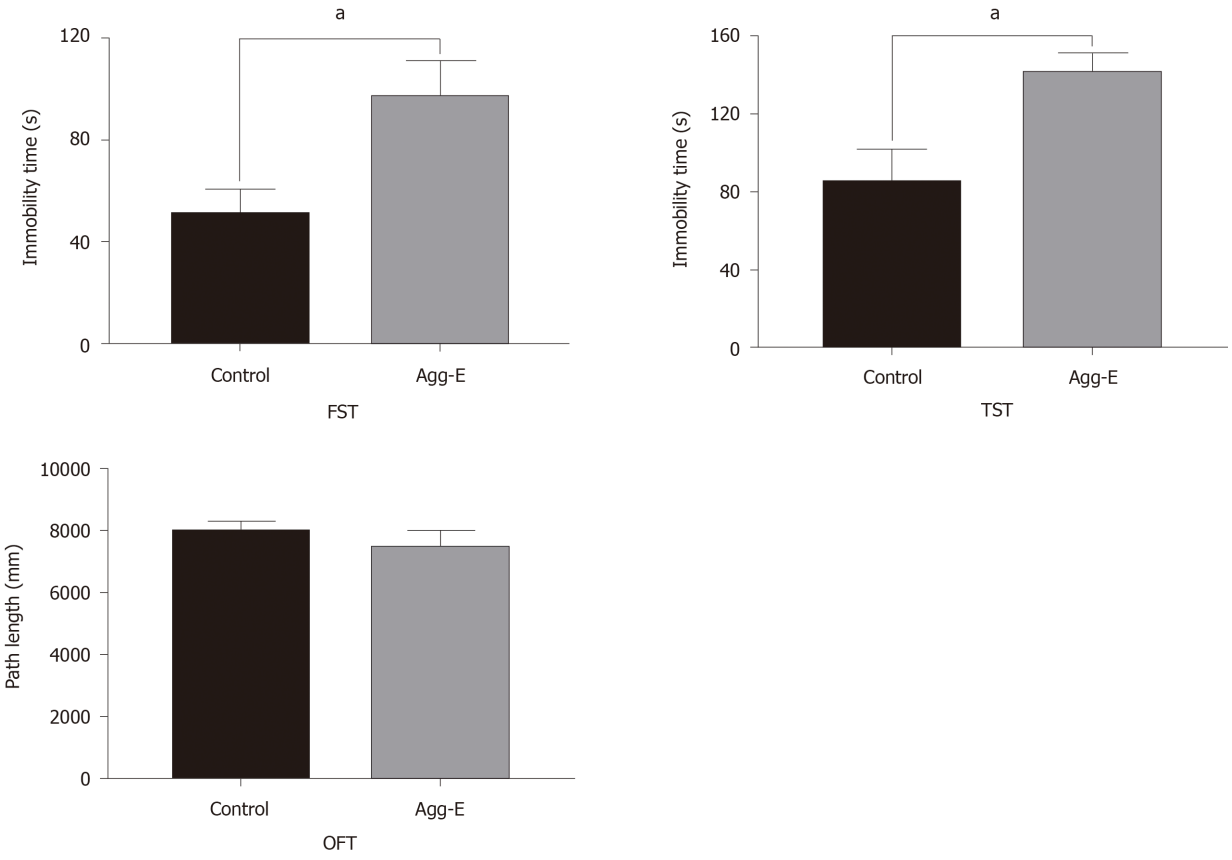


Figure 6 The immobility time in forced swim test and tail suspension test, and the path length of open-field test. Data are presented as the mean ± SD, $^{a}P < 0.05$. Agg-E: Aggressed-exposed; FST: Forced swim test; TST: Tail suspension test; OFT: Open-field test.

cell proliferation and inflammatory responses. It has been known that the MAPK pathway is activated by neuropeptide oxytocin in the paraventricular nucleus of the hypothalamus by transactivation of EGFR to regulate anxiety[35]. Interestingly, the connections among hub genes and relevant pathways were supported by the results of the co-occurrence analysis of test mining. We found that the above genes were correlated with the enriched signaling pathways. It indicated that these altered hub genes played functional roles in PTSD *via* these pathways. Based on the evidence above, we argued that these genes may serve as important contributors to PTSD. Besides, the depression-like behavioral data (FST and TST) indicated a marked increase in immobility time in the Agg-E group. It showed that stress exposure could induce depressive-behavior that may co-occur with PTSD.

CONCLUSION

In conclusion, the present study identified a series of significantly expressed genes and relevant pathways, which may serve as potential biomarkers involved in the pathogenesis of PTSD. The results were confirmed using experimental verification. We further surmised that the identified genes may be key contributors associated with PTSD. However, future studies on the precise mechanism are warranted.

ARTICLE HIGHLIGHTS

Research background

Post-traumatic stress disorder (PTSD) is a common trauma-related or stressor-related disorder characterized by a wide range of significant symptoms, *e.g.*, avoidance, negative emotion, and hyperarousal. A variety of targeted genes and pathways may be associated with the occurrence and progression of PTSD.

Research motivation

The underlying mechanisms of PTSD are complicated and not entirely clear. We sought to uncover the key targets for the potential mechanisms associated with PTSD at the molecular level.

Research objectives

The main objective was to identify critical genes and key pathways associated with PTSD.

Research methods

Our study was conducted based on the NCBI Gene Expression Omnibus database by using bioinformatics analysis. The differentially expressed genes were identified by using GEO2R. Gene functional annotation and pathway enrichment were performed using the Database for Annotation, Visualization, and Integrated Discovery. The gene-pathway network was mapped with Cytoscape software. Quantitative real-time polymerase chain reaction (qRT-PCR) analysis was applied for validation, and text mining by Coremine Medical was used to confirm the connections among genes and pathways.

Research results

A total of 358 upregulated genes and 615 downregulated genes were obtained. These altered genes were significantly enriched in PTSD-related pathways, such as MAPK, Ras, and ErbB signaling pathways. The co-expression pattern of these enriched pathways with their genes was constructed. And a group of hub genes was obtained from the gene-pathway network. qRT-PCR indicated that the hub genes were differentially expressed. Besides, text mining showed that these genes were linearly connected with the associated pathways, which suggested that these genes might play crucial roles in the signal pathway conduction in the onset and development of PTSD.

Research conclusions

The results of this study have contributed to the identification of a panel of candidate genes and important pathways, which may serve as potential biomarkers involved in the pathogenesis of PTSD.

Research perspectives

Our findings may provide a significant step forward in understanding the pathogenesis of PTSD at the molecular level.

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