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ABSTRACT

BACKGROUND: Anxiety and depressive disorders are the most common mental disorders. Detecting a disorder at an early stage can prevent the development of severe disorders and preserve the patient's functioning ability. Simple and reliable screening tools based on self-completion of questionnaires can be used for this purpose. However, it is not always the case that the scores of the self-questionnaire align with those of the clinician.

AIM: To estimate the prevalence of anxiety-depressive disorders using the GAD-7 and HADS self-report questionnaires compared to psychiatrist assessment.

METHODS: The study included individuals aged 18 to 65 years, living in Moscow, Russia, without psychiatric disorders, who participated in an online study using the HADS (Hospital Anxiety and Depression Scale, HADS-A and HADS-D) and GAD-7 (Generalized Anxiety Disorder 7-item scale). Anxiety disorder was diagnosed when the total score was ≥10 on the GAD-7 and/or ≥10 on the HADS-A scale, and depression was defined when the total score was ≥9 on the HADS-D scale. Then, 82 randomly selected participants attended an anonymous consultation with a psychiatrist.

RESULTS: The study included 1,097 individuals (72% female), median age 29 (23; 37) years. As a result of testing, anxiety disorder was found in 168 (15%); depressive disorder — in 152 (14%) respondents. At medical verification, anxiety was diagnosed in 18 (22%); depression — in 19 (23%) people. The sensitivity of the HADS-D subscale for physician-diagnosed cases of depression was 61%, and specificity was 73%. The sensitivity of the HADS-A and GTR-7 subscale in identifying cases of anxiety disorder was 58%, specificity 59%. Sixteen percent were first diagnosed with a personality disorder or schizotypal disorder.

CONCLUSION: The level of anxiety and depression in our sample of the population of Moscow, Russia, was higher than the global level. Self-assessment based on the questionnaire seems to not fully reflect the real state of a patient, as evidenced by the differences with the psychiatrist's assessment.

АННОТАЦИЯ

ВВЕДЕНИЕ: Тревожные и депрессивные расстройства — наиболее распространенные психиатрические заболевания. Выявление патологии на ранней стадии может предотвратить развитие серьезных нарушений и сохранить работоспособность пациента. В этом могут помочь простые и надежные скрининговые инструменты, основанные на самостоятельном заполнении опросников. Однако не всегда оценки самоопросника совпадают с клинической оценкой специалиста.

ЦЕЛЬ: Оценить распространенность тревожно-депрессивных расстройств с помощью госпитальной шкалы тревоги и депрессии (Hospital Anxiety and Depression Scale, HADS) и самоопросника генерализованного тревожного расстройства (Generalized Anxiety Disorder-7, GAD-7) и сравнить результат с клиническим заключением психиатра.

МЕТОДЫ: В исследование включили лиц без психических расстройств от 18 до 65 лет, проживавших в г. Москве, которые приняли участие в онлайн-опросе с применением шкал HADS (HADS-A и HADS-D) и GAD-7. Тревожное расстройство определяли при суммарной оценке ≥10 баллов по GAD-7 и/или ≥10 баллов по шкале HADS-A, депрессию — при ≥9 баллов по шкале HADS-D. Затем 82 случайно отобранных участника прошли анонимную консультацию психиатра.

РЕЗУЛЬТАТЫ: В исследование включили 1097 человек (72% женщины), средний возраст 29 (23; 37) лет. В результате тестирования тревожное расстройство обнаружено у 168 (15%), депрессивное расстройство — у 152 (14%) опрошенных. По результатам врачебной диагностики тревога диагностирована у 18 (22%), депрессия — у 19 (23%) человек. Чувствительность подшкалы HADS-D в отношении случаев депрессии, диагностированных врачами, составила 61%, специфичность — 73%. Чувствительность подшкалы HADS-A и GAD-7 при выявлении случаев тревожного расстройства составила 58%, специфичность 59%. У 16% впервые диагностировали расстройства личности или шизотипическое расстройство.

ЗАКЛЮЧЕНИЕ: Уровень тревоги и депрессии в данной выборке из популяции г. Москва оказался повышен. Самооценка по опроснику не в полной мере отражает реальное состояние человека, о чем свидетельствуют несоответствия с оценкой психиатра.

Keywords: *depression; anxiety; urban population; GAD-7; HADS*
Ключевые слова: *депрессия; тревога; городская популяция; GAD-7; HADS*

INTRODUCTION

Today, anxiety and depressive disorders are becoming increasingly relevant, particularly in urban areas. These conditions are largely the result of the ongoing social, economic, and other challenges of our time [1]. It is estimated that over 300 million people worldwide (4.05% of the global population) suffer from anxiety [2], while around 280 million (3.8% of the population) experience depressive disorders.[1] According to the Institute for Health Metrics and Evaluation, in Russia, approximately 5,453,800 people (about 3.8%) are affected by depressive disorders, and 4,999,400 people (about 3.5%) suffer from anxiety disorders. These mental health conditions are among the most widespread in the general population.[2]

The World Health Organization (WHO) predicts that the prevalence of these disorders will rise significantly, with depressive disorders projected to become one of the most common types of disorders by 2030.[3] The highest rates of anxiety and depressive disorders are borne by adolescents [3] and young adults — an active and working population. Recent data from 2022–2023 likewise show an increase in the prevalence of these disorders in Russia.[4] In the ESSE-RF study, clinical depression on the Hospital Anxiety and Depression Scale (HADS) ≥11 points was observed in 4.5% of the study cohort (men — 3.4% and women — 5.4%); and anxiety, in 6.8% (men — 4.0% and women — 5.4%) [4].

Chronic anxiety and depressive disorders can indirectly contribute to the development of various somatic conditions, such as gastrointestinal disorders, allergic reactions, respiratory issues, cardiovascular diseases, frequent headaches, migraines, etc. Early detection of these mental health disorders can prevent the onset of more serious complications and help maintain a patient's overall ability to function [5]. Additionally, whenever a patient voices somatic complaints, it is important to rule out underlying anxiety or depression [6].

Therefore, simple and reliable screening tools for these conditions are essential. Screening can be effectively conducted using psychometric self-assessment scales [7], which provide a quick and easy method of preliminary diagnosis.

Among the most commonly used self-assessment scales are the HADS [8] and the Generalized Anxiety Disorder 7-item scales (GAD-7) [9]. These tools have been validated for identifying anxiety and depressive disorders in patients with various conditions, including cancer [10], heart disease [11, 12], neuropsychiatric disorders [13], and irritable bowel syndrome [14]. While the GAD-7 scale has not been officially validated in Russia, a Russian-language version has been adapted [15]. In 2023, the validation results of the Russian-language version of the HADS scale were published [16].

Based on studies involving different cohorts, the prevalence of anxiety, as measured on the HADS-A scale, was found to be 26% among cancer patients [17], 12% in patients with coronary heart diseases [18], 16% in those with cardiovascular diseases or diabetes [19], 14% in patients with irritable bowel syndrome, and 11% in those with chronic thromboembolic pulmonary hypertension, according to the GAD-7 scale [20]. The prevalence of depression according to the HADS-D scale was 28% in the cancer cohort [17], 20% in patients with irritable bowel syndrome [20], and 28% in patients with cardiovascular diseases or diabetes [19]. The authors observed comparable levels of anxiety in individuals with coronary heart diseases when compared to a European sample assessed using the same protocol, while they noted a higher incidence of depression in the Russian population [18]. In a previous study, we had evaluated anxiety levels among healthcare workers, revealing an increase from 16.09% in 2020 to 39.08% in 2022, alongside a rise in depression from 8.05% to 13.79%. This increase in anxiety severity contrasts with findings from earlier longitudinal studies [21].

However, the previous study had a limitation in that anxiety and depression were measured using self-reported scales (HADS), which may be prone to bias or inaccuracies due to the subjective nature of the responses. Self-assessments can also be misleading since anxiety symptoms may resemble those of somatic diseases, potentially leading to an underestimation of anxiety levels. Additionally, these symptoms can overlap with those of other mental health conditions [22]. To address potential inaccuracies stemming from this limitation, we added an additional

[1] World Health Organization (WHO). Depressive disorder (depression). Available from: https://www.who.int/news-room/fact-sheets/detail/depression

[2] About 4 million Russians suffer from mental disorders. In Russian. Available from: https://www.interfax.ru/russia/945840

[3] Global status report on physical activity 2022. Available from: https://iris.who.int/bitstream/handle/10665/363607/9789240059153-eng.pdf?sequence=1

[4] Quarterly forecast of GDP. In Russian. Available from: https://ecfor.ru/publication/kvartalnyj-prognoz-ekonomiki-vypusk-55

anxiety scale, the GAD-7, and evaluated the prevalence of anxiety and depressive disorders in a random sample of patients who had undergone psychiatric consultations.

Therefore, the aim of this study was to assess the prevalence of anxiety and depressive states using self-reported questionnaires in a sample of Moscow residents, followed by a comparison of these self-assessments with a psychiatrist's diagnosis.

METHODS

Study design

We conducted a cross-sectional study to assess the prevalence of anxiety and depression using screening scales, followed by clinical (physician) validation of the respondents' mental states.

Setting

The study involved 1,097 male and female participants aged 18 to 65, recruited from the Moscow population between June 2022 and September 2023.

Participants

Participants were volunteers who had responded to an invitation on social media to participate in an examination for mental disorders. Individuals with a previously diagnosed mental disorder or severe somatic diseases were excluded. The announcement provided information about the study's goals and objectives, study site, and eligibility criteria. Participants received the testing materials electronically via the Google Forms online tool (Google LLC, USA). They were asked to provide their sex, age, education level (none, primary, incomplete secondary, complete secondary, higher, academic, or degree postgraduate), place of residence, and respond to questions from the GAD-7 and HADS scales. Each participant could submit their information only once during a single session, after which they could not revisit the study results. However, participants were allowed to revise their answers while filling out the electronic form; leaving any questionnaire items blank was not permitted.

Next, 100 individuals who responded to the online questionnaire were randomly selected using the Lotto function in Excel VBA for this study. They were contacted by phone and invited to participate in a free, anonymous in-person consultation with a psychiatrist. Potential participants were informed that the consultation aimed to verify the results of the psychometric testing conducted for research purposes. If they agreed to participate, they were given the option to select a convenient date from the available slots for a visit.

At the time of the consultation, physicians, like the study participants, were unaware of the psychometric testing results. Based on the consultation outcomes, doctors diagnosed any mental disorders present in the subjects according to ICD-10 criteria.[5]

Anxiety and depression assessment scales

In this study focused on developing a method for assessing the risk of mental disorders, psychometric testing was performed using the GAD-7 and HADS scales, both adapted into Russian. The GAD-7 scale (sensitivity 89%, specificity 82% [23]) consists of seven items, each with four response options ranked from 0 to 3 points based on the severity of anxiety symptoms [24]. The HADS scale includes two subscales: anxiety (HADS-A, specificity 94.0%, sensitivity 73.8%) and depression (HADS-D, sensitivity 72.9%, specificity 92.5%) [25]. Each subscale consists of seven items with four answer options that reflect the severity of symptoms, ranging from 0 (absence) to 3 (maximum severity) [26]. Anxiety was identified with a total score of ≥10 points on the GAD-7 [23] scale and/or ≥10 points on the HADS-A scale, while depression was indicated by a score of ≥9 points on the HADS-D scale [27].

Statistical analysis

The data were analyzed using the IBM SPSS Statistics software, version 26.0 (IBM, USA). Quantitative parameters were described by reporting the median along with the 25th and 75th percentiles. Anxiety and depression scores in independent groups were compared using the Kruskal-Wallis test (H-test) for three or more groups and the Mann-Whitney test (U-test) for two groups. The Pearson's chi-squared test was used to compare frequencies in independent groups. To evaluate the internal consistency of the HADS and GAD-7 scales, Cronbach's alpha coefficient was calculated (where a value of 1 indicates perfect consistency, >0.9 indicates very good consistency, >0.8 indicates good consistency, >0.7 indicates acceptable consistency, >0.6 indicates questionable consistency, >0.5 indicates poor consistency, and <0.5 indicates insufficient consistency). Differences were considered statistically significant at p <0.05.

[5] Mental and behavioral disorders related to substance use (F10-F19). In Russian. Available from: http://mkb-10.com/index.php?pid=4048

Ethical approval

Written informed consent was obtained from each potential participant for the use of their data for research purposes. After the consultation with a psychiatrist, all participants received the results of the psychometric assessments. The results from the psychiatrist's consultation were kept confidential and were not disclosed to the participants. The study protocol was approved by the local ethics committee of Mental-health clinic No.1 named after N.A. Alexeev, Moscow, Russia (protocol No.1 dated January 25, 2022).

RESULTS

Sample characteristics

The database used in this study to develop a method for assessing the risk of developing a mental disorder included information from 1,097 participants, with 794 (72%) being women. The median age of the respondents was 29 years (interquartile range: 23 to 37 years). At the time of the study, 841 (77%) individuals had higher education, which included 69 participants with an academic degree, 153 (14%) with complete secondary education, and 12 (1%) with incomplete secondary education, and 91 (8%) participants did not provide information regarding their education. The median anxiety score on the GAD-7 scale was 4 points (2; 7), while the median score on the HADS-A anxiety scale was 6 points (3; 9), and on the HADS-D depression scale, it was 4 points (2; 7). Anxiety disorder was identified in 163 (14.86%) participants according to the GAD-7 scale (≥10 points) and in 164 (14.9%) according to the HADS-A scale (≥10 points). At least one of these scales indicated anxiety in 168 (15.3%) participants. Depression, as measured by the HADS-D scale (≥9 points), was found in 152 (13.86%) respondents.

Clinical assessment of anxiety and depression

A random selection of 82 individuals underwent an anonymous consultation with a psychiatrist. The individuals who were not part of this random sample but had also consulted a psychiatrist were comparable to the rest of the study participants in terms of age, sex, and education level (see Table 1).

Based on the psychiatrists' evaluations, among the 82 participants who had undergone consultation, 32 (39%) were deemed mentally healthy. Affective disorders characterized by a predominant depressive syndrome (referred to as "depressive disorders") were identified in 19 participants (23%). Neurotic disorders with a predominance of anxiety symptoms ("anxiety disorders") were found in 18 participants (22%), while other mental disorders were diagnosed in 13 participants (16%) (Figure 1).

Table 1. Characteristics of random sample participants

Parameters	Group not included in the random sample (*n*=1,015)	Random sample (*n*=82)	U	*p*-value
Age, years	29 (23; 37)	27 (22; 31)	30430	0.07
Sex (female), abs. (%)	730 (72%)	64 (78%)	1.24	0.27
Education (higher), abs. (%)	778 (77%)	63 (77%)	3.16	0.08
Academic degree, abs. (%)	62 (6%)	7 (8%)	0.64	0.43
Complete secondary education, abs. (%)	141 (14%)	12 (15%)	0.03	0.86

The proportion of individuals displaying depressive symptoms was consistent between the test results and the psychiatrist's evaluation (χ^2=3.02; p=0.083). Among the 18 patients diagnosed with depression by the psychiatrist, 11 showed corresponding results on the psychometric test, yielding a sensitivity index of 61%. Of the 64 patients who were not diagnosed with depression by the psychiatrist, only 17 produced positive test results (a specificity of 73%). There was a discrepancy between the test results and the psychiatrist's assessment for 24 individuals (29%) (Table 2). The proportion of individuals exhibiting anxiety symptoms differed significantly from the psychiatrist's evaluation (χ^2=8.8; p=0.004), with a sensitivity of 58% and a specificity of 59%. There was a discrepancy between the test results and the psychiatrist's assessment for 34 individuals (41%) (Table 3).

The assessment of internal consistency showed good consistency of the scales, except for the assessment of anxiety in the group of people with other mental disorders (Table 4).

Then, the anxiety and depression scores on the scales in the groups of patients with different clinical diagnoses were compared. No such differences were found for the GAD-7 and HADS-A scales. Statistically significant differences between the groups when comparing them were found for the depression score on the HADS-D scale (Table 5).

DISCUSSION

In a study of a random sample of 1,097 people living in Moscow who responded to an invitation on social media

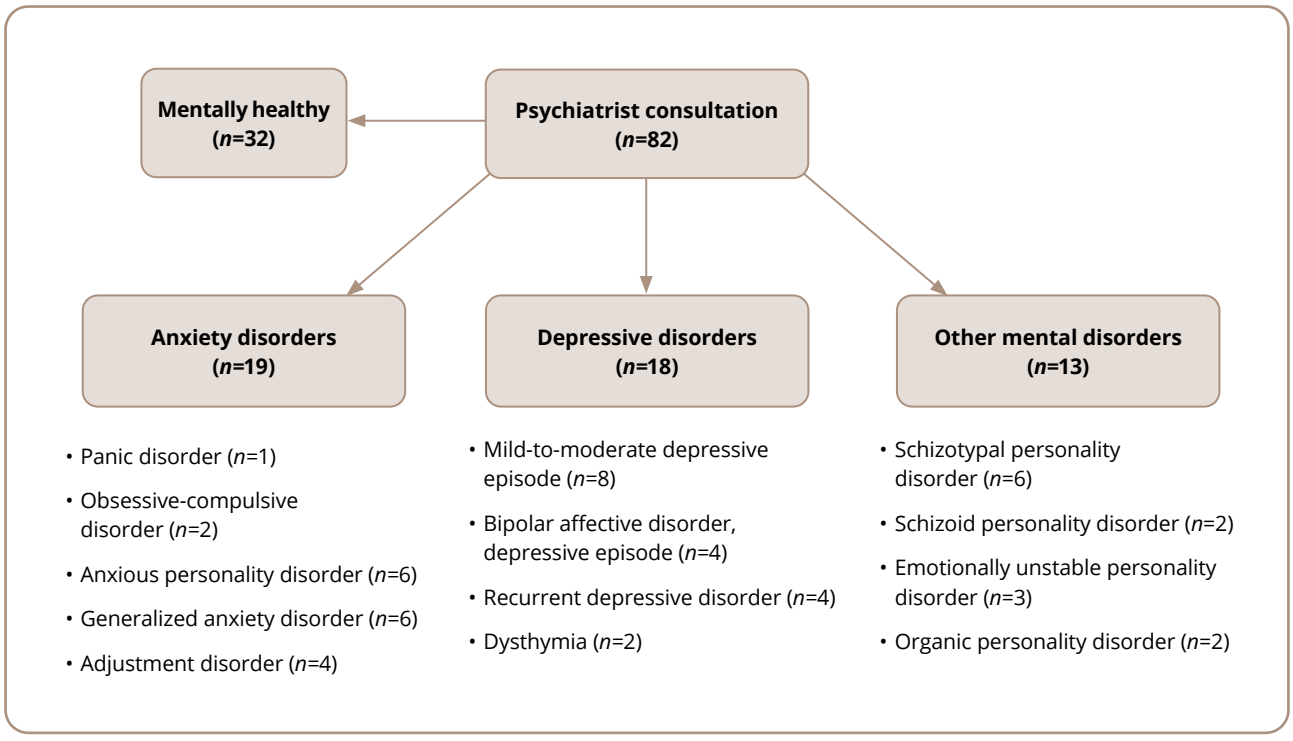

Figure 1. Diagnoses in the sample after clinical assessment.

Source: Savenkova et al., 2024

to participate in a scientific study of mental health, the proportion of people with an anxiety disorder was 14.9%, and this rate was similar for both scales under study (GAD-7 and HADS-A). The proportion of participants showing signs of depression, based on the HADS-D self-assessment, was 13.86%. These rates exceed the global averages, as demonstrated in previous studies conducted in Russia [7]. In comparison, during the COVID-19 pandemic, similar research found that anxiety and depression rates in a comparable sample were 14% and 8%, respectively [28]; thus, the prevalence of anxiety disorders remained steady while the proportion of depressive disorders increased. When comparing the current findings with previous studies conducted on healthcare professionals, the prevalence of depressive disorders was nearly identical (13.79% vs 13.86%). However, anxiety disorders were significantly lower in the general population (14.86%) compared to that in healthcare professionals (39.08%).

Both the GAD-7 and HADS scales, used to assess anxiety and depressive states, are brief, easy-to-complete self-questionnaires. Although the GAD-7 and HADS scales were developed to identify anxiety and depressive disorders in patients with mental or somatic disorder, there are a significant number of publications on their use in

Table 2. Comparison of psychometric testing results and clinical assessment of depressive disorder

Psychometric testing	Clinical (physician) assessment		Total
	Depression (–)	Depression (+)	
Depression (–)	47 (57%)	7 (9%)	54 (66%)
Depression (+)	17 (21%)	11 (13%)	28 (34%)
Total	64 (78%)	18 (22%)	82 (100%)

Note: (–) — absence of depression, (+) — presence of depression; (–)/(+) — for the test results, the presence of a depressive disorder was established with a total score of ≥9 points on the HADS-D scale.

Table 3. Comparison of psychometric testing results and the clinical assessment of anxiety disorder

Psychometric testing	Clinical (physician) assessment		Total
	Anxiety (–)	Anxiety (+)	
Anxiety (–)	37 (45%)	8 (10%)	45 (55%)
Anxiety (+)	26 (32%)	11 (13%)	37 (45%)
Total	63 (77%)	19 (23%)	82 (100%)

Note: (–) — absence of anxiety disorder, (+) — presence of anxiety disorder; (–)/(+) — for the test results, the presence of anxiety disorder was established with a total score of ≥10 points on the GAD-7 scale and/or ≥10 points on the HADS-A scale.

Table 4. Internal consistency (Cronbach's alpha) of the scales in the groups with different medical assessments of mental health

Mental health*	Scales		
	GAD-7	HADS-A	HADS-D
Mentally healthy	0.916	0.850	0.835
Anxiety disorders	0.882	0.733	0.873
Depressive disorders	0.819	0.911	0.868
Other mental disorders	0.676	0.683	0.967

Note: *Based on the results of the clinical assessment. GAD-7 — Generalized Anxiety Disorder 7-item scale; HADS — Hospital Anxiety and Depression Scale.

Table 5. Comparison of anxiety and depression scores on self-administered questionnaires in the groups with different clinical assessments of mental health

Scales	Mental health assessment by a specialist				H	*p*-value
	Mentally healthy (*n*=32)	Anxiety disorders (*n*=18)	Depressive disorders (*n*=19)	Other mental disorders (*n*=13)		
GAD-7 Me [Q1;Q3]	4.5 [3.0; 8.25]	9.0 [4.0; 13.5]	12.5 [6.25; 13.0]	5.0 [2.0; 11.0]	7.60	0.06
HADS-A Me [Q1;Q3]	7.0 [4.75; 9.25]	10.0 [5.0; 12.0]	12.50 [8.5; 15.5]	6.0 [4.0; 12.0]	7.57	0.06
HADS-D Me [Q1;Q3]	4.0 [2.0; 8.0]	6.0 [2.5; 10.5]	11.0 [5.25; 13.0]	6.0 [4.0; 8.0]	8.00	0.05

Note: GAD-7 — Generalized Anxiety Disorder 7-item scale; HADS — Hospital Anxiety and Depression Scale.

the general population. Table S1 in the Supplementary summarizes findings from some of these studies.

Variations in the estimated prevalence of anxiety and depressive disorders across studies can often be attributed to differences in the cutoff values used. In 2023, the Russian-language version of the HADS scale was validated for the Russian population, establishing cutoff values for detecting clinically significant forms of these disorders [16], which we applied in our study.

The participants in our study were predominantly young, with a median age of 29 years. While most research indicates that the risk of anxiety and depressive disorders tends to increase with age [29], recent evidence suggests that these disorders are increasingly affecting younger populations [30, 31].

The use of screening scales can be challenging, because results may be overestimated due to factors such as hypochondriasis, personality traits, and the subjective interpretation of questions by respondents. Sato and Kawahara (2011) found that memory tends to be selective for negative emotional states like anxiety, depression, and helplessness. The authors observed that individuals often overemphasize the significance of past negative experiences, which was evident in the comparison of retrospective assessments with daily ones [32]. These findings are partly supported by results from Howren and Suls, who showed that individuals in an anxious mood reported more concurrent symptoms, while those in a depressed mood recalled more past symptoms [33]. Taple et al. (2019) also discovered that short anxiety and depression questionnaires, such as PROMIS, may be difficult for individuals with low health literacy. People with limited health literacy may respond differently to anxiety and depression questions compared to those with higher health literacy [34]. In 2023, a study with 30 adolescents (aged 15 to 17) who completed the GAD-7 scale every three weeks over a period of year found that individuals with identical GAD-7 scores experienced different dynamics of symptoms [35]. This suggests that symptom patterns are variable and dynamic, and that to gain a full understanding of a patient's clinical presentation, it is important to consider both the progression of symptoms over time and consult specialists to verify the diagnoses.

In our study, 82 participants from the total sample underwent an anonymous psychiatric consultation, which allowed us to divide them into four groups: 39% had

no mental disorders, 23% had affective disorders with predominant depressive symptoms, 22% had neurotic disorders with predominant anxiety symptoms, and 16% had other mental disorders. Notably, the proportion of anxiety disorders diagnosed by psychiatrists was higher than what was indicated by the self-assessment questionnaires.

It is also important to highlight that 13 participants (16%) received psychiatric diagnoses for the first time, falling into the categories of schizophrenia spectrum disorders and personality disorders. In the general population, approximately 8% have personality disorders [36], and around 1% have schizophrenia spectrum disorders [37]. Several factors could explain why such a high percentage of individuals with these diagnoses was identified in our study, especially since the participants had initially denied having any previously diagnosed mental disorders. Stigma surrounding mental health may cause people to feel ashamed or fearful of consulting a psychiatrist [38]. More broadly, lack of information, fear of judgment, and limited access to care are common reasons why people avoid seeking mental health services. However, distress from undiagnosed mental conditions may have motivated these individuals to engage in online testing and subsequently attend an in-person psychiatric consultation in our study.

The evaluation of the internal consistency of the GAD-7 and HADS questionnaire items showed that the respondents did not provide random answers. The lowest level of consistency, which indicated sufficient but not strong reliability, was observed in the anxiety scales (GAD-7 and HADS-A) for individuals diagnosed with personality disorders and schizophrenia spectrum disorders.

However, no significant differences in internal consistency for anxiety and depression assessments across the clinical groups identified by psychiatrists were found. This suggests that the participants provided thoughtful responses, reflecting their actual conditions rather than responding haphazardly. When comparing scale scores, there were significant differences in depression scores for individuals with a clinical diagnosis of depressive disorder, but no significant differences in anxiety scores across the clinical groups. Anxious affect may be a clinical symptom of depressive disorders [39]. When filling out self-assessment questionnaires, patients often report a feeling of anxiety, while depressive symptoms may take a backseat, either due to a lack of subjective complaints or because the clinical features of depression are not fully captured by the screening questions. The clinical differentiation of anxiety and depressive disorders is a challenging task. Anxiety may be seen by clinicians as a feature of depression rather than a standalone disorder. In addition, the two conditions may also coexist as comorbidities [40]. The diagnosis may depend on the psychiatrist's experience and training, influencing whether they interpret the patient's symptoms as an independent anxiety disorder or as depression with an anxious affect [41]. Additionally, the use of ICD-10 criteria is known to be associated with a lower reliability in diagnosing anxiety disorders [42].

A limitation of this study is the biased sample. The study involved residents of a large metropolitan area, with a sample characterized by a high proportion of women, individuals with higher education, and those with mental disorders, as identified by the psychiatrists who consulted the participants. People who are interested in their mental health and take part in such studies are more likely to either have or suspect they have a mental disorder. However, it is very difficult to overcome this limitation and many studies relying on volunteers for participation face similar biases. Furthermore, in different regions of Russia, various economic, socio-demographic, and environmental factors may take precedence in influencing mental health, which may result in different findings [43, 44]. In large cities like Moscow, however, anxiety and depressive disorders are particularly prevalent. The limitations of online testing, as noted in previous research, also apply to this study [28].

CONCLUSION

The anxiety and depression levels among a random sample of Moscow residents who participated in an online mental health study were found to exceed global averages, reaching approximately 14%.

The proportion of individuals with depressive symptoms, as measured by scales, was similar to the clinical evaluations conducted by psychiatrists, while the assessments of anxiety symptoms were overestimated based on the test results.

Early diagnosis of anxiety and depressive disorders is a critical issue, and while self-administered screening scales can help address the problem, their reliability remains limited.

Future research should concentrate on the development of integrated approaches that combine the ease and accessibility of psychometric tools with the precision of clinical interviews.

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Dynamics of Clinical Manifestations and Social Functioning in Schizophrenia: A Non-interventional Observational Study of Paliperidone Palmitat Dosage Forms

Динамика клинико-психопатологических проявлений и качества социального функционирования пациентов с шизофренией, получающих палиперидон пальмитат в разных лекарственных формах: неинтервенционное наблюдательное исследование

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Original research

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ABSTRACT

BACKGROUND: Over the past seven years, the use of long-acting forms of antipsychotic medication has significantly increased in Russia. Specifically, in Moscow, from 2016 to 2021, the proportion of prescribed injectable long-acting antipsychotics had increased more than sevenfold (from 3% to 23%). Studies have shown that the correct selection of target groups for such therapy can reduce the frequency of relapses requiring hospitalization, lower the costs of inpatient care, and shift the focus of therapy from multiple drug administrations to psychosocial work.

AIM: This study was aimed at evaluating changes over time in psychosocial functioning, as well as clinical and psychopathological manifestations, in patients with schizophrenia during early remission and while on therapy with different forms of paliperidone: oral paliperidone (OP), paliperidone palmitate administered once monthly (PP1M), and paliperidone palmitate administered once every three months (PP3M).

METHODS: The observational study included 155 patients: 54 patients who had been treated with another second-generation antipsychotic received OP, 50 patients who had been treated with another antipsychotic received PP1M injections, and 51 patients who had been in remission for four months after treatment with PP1M received PP3M. The duration of the follow-up period was 12 months. Assessment of personal and social functioning was conducted five times: before the start of treatment, and 3, 6, 9, and 12 months later.

RESULTS: Treatment in all groups led to a statistically significant reduction in the severity of positive symptoms (p <0.001). Hallucinations proved more susceptible to therapy (p <0.001), while persistent delusions showed greater treatment resistance. Significantly more patients in the PP1M and PP3M groups had completed the entire program (n=24; 48.0%, and n=30; 58.8%, respectively) compared to the OP group (n=11; 20.4%). The PP3M group demonstrated the highest treatment adherence, with the largest number of patients completing the study, and a similar rate of exacerbations or inadequate efficacy compared to the other groups.

CONCLUSION: Treatment with different forms of paliperidone provides a roughly equal pace reduction in the severity of schizophrenia, including positive and negative symptoms. The PP3M group had better adherence and the highest number of patients who fully completed the study.

АННОТАЦИЯ

ВВЕДЕНИЕ: За последние семь лет в России отмечается заметный рост применения пролонгированных форм антипсихотиков. В частности, в Москве с 2016 по 2021 годы доля инъекционных форм пролонгированных антипсихотиков увеличилась более чем в 7 раз (с 3% до 23%). Исследования показали, что правильный выбор целевых групп для такой терапии может уменьшить частоту рецидивов с госпитализацией, снизить затраты на стационарную помощь и сместить акцент терапевтической помощи от многоразового приема препаратов к психосоциальной работе.

ЦЕЛЬ: Изучение динамики психосоциального функционирования и клинико-психопатологических проявлений у пациентов с шизофренией в период становления ремиссии на фоне терапии различными формами палиперидона: пероральной формой палиперидона (ПО), палиперидона пальмитатом для введения один раз в месяц (ПП1М) и палиперидона пальмитатом для введения раз в три месяца (ППЗМ).

МЕТОДЫ: В наблюдение были включены 155 пациентов: 54 пациента после лечения другим антипсихотиком второго поколения получали палиперидон для перорального применения (ПО), 50 пациентам после лечения другим антипсихотиком были назначены инъекции ПП1М, 51 пациенту после купирования обострения и 4 месяцев лечения ПП1М назначались инъекции ППЗМ. Период наблюдения составил 12 месяцев. Оценка личностного и социального функционирования проводилась пять раз: до начала лечения, спустя 3, 6, 9 и 12 месяцев.

РЕЗУЛЬТАТЫ: Терапия во всех группах привела к статистически значимому снижению выраженности позитивных симптомов (p <0,001). При этом более чувствительными к терапии оказались галлюцинации (p <0,001), тогда как остаточный бред оставался более устойчив к терапии. В группе ПП1М и ППЗМ больше пациентов полностью завершили программу исследования (n=24, 48,0% и n=30, 58,8% соответственно) по сравнению с группой ПО (n=11, 20,4%). При этом в группе ППЗМ отмечалось наилучшее следование назначенной схеме терапии, максимальное число пациентов, полностью завершивших исследование, равное с другими группами количество случаев обострений или недостаточной эффективности.

ЗАКЛЮЧЕНИЕ: Терапия различными лекарственными формами палиперидона обеспечивает примерно равный темп и интенсивность редукции общей тяжести шизофрении, позитивных и негативных симптомов. В группе ППЗМ наблюдалось лучшее соблюдение назначенной схемы терапии и наибольшее количество пациентов, полностью завершивших исследование.

Keywords: *paliperidone palmitate; acute schizophrenia; remission of schizophrenia; psychosocial functioning; long-acting injectable antipsychotics*
Ключевые слова: *палиперидона пальмитат; обострение шизофрении; ремиссия шизофрении; социальное функционирование; пролонгированная форма антипсихотика*

INTRODUCTION

The use of long-acting injectable antipsychotics (LAIs) represents an effective treatment option for schizophrenia, which helps overcome patient suboptimal adherence to prescribed therapy, leading to disease relapses [1–12]. While previously long-acting forms were typically prescribed for the chronic disease, when relapse of psychosis was already imminent, clinical experience and recent scientific research have shown that LAIs represent an effective treatment strategy for patients in the early phase or in the first episode of the disease, where preventing relapses brings the greatest benefit [2, 4, 12]. However, LAI have been underutilized in global practice for a long time and, until recently, in domestic clinical practice as well [13–16]. Unfortunately, the most common reason for the neglect of LAI prescriptions is the lack of knowledge and the persistent beliefs of physicians that long-acting forms are associated with a higher risk of adverse effects (AEs) and the difficulty in managing them. There is also the real issue that the most modern long-acting forms are expensive and may be inaccessible for widespread use in clinical practice [2].

Despite existing contradictions regarding the benefits and risks and inconsistent results from randomized controlled trials (RCTs) [17–22], most studies — both RCTs and naturalistic — demonstrate the efficacy of treating schizophrenia with long-acting formulations of paliperidone [23–38]. It has been noted that paliperidone palmitate reduces the severity of positive and negative symptoms, hostility, aggression, and exerts a pro-cognitive effect [25, 26, 35, 39–41].

LAI forms of paliperidone have demonstrated anti-relapse effects, as evidenced by RCTs, meta-analyses, and observational studies of various durations [3, 4, 28, 30–32, 38, 39, 42–48]. Among these, the dosage form of paliperidone for administration once every three months (PP3M) most effectively reduces relapse rates requiring hospitalization and contributes to stabilizing remission. This is supported, among other findings, by the extended time between the discontinuation of the drug and the onset of exacerbation [16, 26, 30, 35, 36, 40, 48]. Research into the effectiveness of LAI forms of paliperidone has identified practical predictors of sustained remission. In particular, these include a one-point reduction in the Marder factor of negative symptoms on the Positive and Negative Syndrome (PANSS) scale [49], a one-point decrease on the Clinical Global Impression (CGI-S) scale, and an increase of 7–10 points in the total score and social functioning score on the Personal and Social Performance (PSP) scale [50]. However, recent meta-analyses do not conclusively show that the anti-relapse effects of LAI paliperidone palmitate are superior to other oral or injectable antipsychotics of both generations [38, 47].

Treatment with LAI paliperidone is associated with better adherence to prescribed therapy compared to first-generation antipsychotics (FGAs) and even oral second-generation antipsychotics (SGAs) [28, 29, 36, 39, 42, 43]. Improved satisfaction with treatment outcomes and adherence to prescribed therapy have been observed even in patients with severe schizophrenia [29, 39], although achieving clinical stabilization in such cases often required higher doses of the drug [29]. Some studies indicate that paliperidone palmitate can replace clozapine in the treatment of resistant schizophrenia [33] and reduce the risk of suicidal behavior [30].

Paliperidone palmitate is generally well tolerated in all its dosage forms [24–26, 28, 29, 39, 51]. Its use reduces the need to frequently prescribe tranquilizers and medication for managing extrapyramidal symptoms, with side effects comparable to placebo [30, 38, 40, 51]. Only a small number of patients discontinue therapy due to AEs, and there is a gradual decrease in the prevalence of moderate and severe AEs over time [16]. Among the AEs, weight gain, hyperprolactinemia, and its associated clinical

manifestations are significantly more frequent than in placebo groups [35, 38, 47].

Several publications highlight the positive impact of LAI paliperidone on the quality of life and social functioning of patients with schizophrenia [26, 36, 40, 41, 45], especially those experiencing their first episode or recently diagnosed [35, 37, 40, 44]. For example, patients with a disease duration of less than 5 years or 6–10 years showed better outcomes compared to those with a disease duration of more than 10 years [26]. Data suggest that early initiation of PP3M improves social functioning, extends remission duration, and contributes to achieving "functional remission", characterized by a return to the previous social status and activities [16, 28, 30, 41, 45, 46, 48, 50, 52, 53].

The introduction of long-acting paliperidone formulations is associated with decreased burden on the health care system, reduced direct and indirect costs, and fewer hospitalizations and doctor visits [43, 54, 55]. High treatment response rates, adherence to therapy, and rapid improvements in social functioning with paliperidone palmitate, countering the well-known challenges of early schizophrenia, such as high relapse potential and poor medication adherence, have led to recommendations to use LAI forms of paliperidone, including PP3M, not only on patients with longer disease duration, but also at the earliest stages of the disorder [4]. This shift in approach has been supported by research [35, 37] and aptly summarized by the biblical phrase "the last shall be first", referenced by Stahl [56] in one of his articles on the use of long-acting antipsychotics.

In Russia, there has been a noticeable increase in the use of long-acting antipsychotics, both FGAs and SGAs ones, over the past seven years [13, 14, 15]. Specifically, in Moscow, from 2016 to 2021, the proportion of LAI antipsychotics used increased more than sevenfold (from 3% to 23%). While long-acting risperidone (LR) dominated among LAI prescriptions in 2013–2015 (76%–77%), the structure shifted from 2016 to 2021, with an increased share of paliperidone formulations. By 2021, the ratio of paliperidone to risperidone formulations was characterized by a predominance of paliperidone palmitate: paliperidone palmitate administered once monthly (PP1M) accounted for 37%; PP3M — for 26%; LR — for 37% [14]. Research has shown that proper selection of target groups for such therapy can reduce relapses requiring hospitalization more than tenfold, lower hospital care costs, and shift the focus of care from controlling the administration of multiple doses of medications to psychosocial work, with an emphasis on the timely identification of relapse risks, motivating recovery, continuing education, and employment [16]. Nevertheless, to clarify and confirm the specifics of the drug's effect on various manifestations of a chronic mental disorder, its social consequences, and its impact on other organs and systems, it is imperative to conduct follow-up studies, including "pragmatic" RCTs, in conditions closest to real-world clinical practice [12, 29, 42].

This study aimed to evaluate the dynamics of psychosocial functioning and clinical-psychopathological manifestations in patients with schizophrenia during the onset of remission on therapy with different forms of paliperidone: oral paliperidone (OP), PP1M and PP3M in dosage forms for injection.

The objectives of the observational program included the following:

- to collect data on the duration of adherence to prescribed maintenance therapy for schizophrenia using long-acting antipsychotic dosage forms compared to oral dosage forms;
- to conduct qualitative and quantitative assessments of the severity of psychotic symptoms over time during treatment with long-acting antipsychotics of varying durations of action compared to oral antipsychotics;
- to conduct qualitative and quantitative assessments of the severity of negative symptoms over time during treatment with long-acting antipsychotics of varying durations of action compared to oral antipsychotics;
- to conduct qualitative and quantitative assessments of the parameters of social functioning over time during treatment with long-acting antipsychotics of varying durations of action compared to oral antipsychotics; and
- to evaluate the frequency, occurrence, and severity of AEs during treatment with long-acting antipsychotics of varying durations of action.

METHODS

Study design

An observational cohort prospective study on the dynamics of clinical manifestations and social functioning in patients with paranoid schizophrenia was conducted at specialized health care and research institutions in

Moscow and the Moscow Region (Russia): Mental-health Clinic No. 1 named after N.A. Alexeev, Mental-health Clinic No. 4 named after P.B. Gannushkin, Moscow Regional Mental-health Hospital No. 5.

Setting

All patients received the therapy of paliperidone or paliperidone palmitate based on clinical needs and in accordance with the current clinical guidelines for schizophrenia treatment in the Russian Federation. The study sample consisted of male and female patients with a confirmed diagnosis of schizophrenia who were prescribed paliperidone as part of their treatment: OP at daily doses ranging from 3 to 12 mg, or PP1M intramuscular injections at approved doses of 50 to 150 mg, or PP3M intramuscular injections at doses of 175 to 525 mg.

Data collection and monitoring for this study covered the observation period from March 18, 2021, to April 11, 2023. The maximum observation period for an individual patient was 12 months (360±7 days).

All patients whose mental state and social functioning dynamics were monitored received comprehensive information about the study and provided written informed consent to be included. The study protocol, patient information materials, informed consent forms, and case report forms were reviewed and approved by the Independent Ethics Committee at Mental-health Clinic No. 1 named after N.A. Alexeev (Meeting minutes No. 01 dated March 1, 2021).

Participants

Inclusion criteria:

All participants

- Diagnosed paranoid schizophrenia according to the International Classification of Diseases 10th Revision (ICD-10) (F20), including F20.00 (continuous course), F20.01 (episodic course with progressive deficit), F20.02 (episodic course with stable deficit), F20.03 (episodic remitting [recurrent] course), F20.09 (observation period of less than one year).
- Male or female patients aged 18 to 65 years inclusive at the time of provision of consent to participate in the study.
- Patients for whom the attending physician determined that oral paliperidone or paliperidone palmitate (administered monthly or every three months via intramuscular injection) was a viable treatment option. The physician's decision to prescribe the medication was based solely on clinical indications, independent of the study design.
- Presence of mild or moderate delusional ideas or hallucinations that did not necessitate intensified therapy or a shift to more intensive mental health care (e.g., hospitalization or a day hospital setting).
- Written informed consent to the collection of socio-demographic and medical data, responses to psychometric scales, and the processing of anonymized socio-demographic and medical data.
- A schizophrenia relapse experienced and resolved 3 to 6 months prior to the study, with treatment resulting in symptomatic improvement, allowing the patient to enter the stabilization and maintenance (anti-relapse) therapy phase by the time of consent.
- Health condition and contraindications: based on medical examination, history, and key vital signs, absence of diseases that, in the physician's opinion and after reviewing the Summary of Product Characteristics (SmPC), would be a contraindication to the use of paliperidone.

Group 1

- The patient received OP treatment for no more than 7 days, and the decision to prescribe OP in any dose was made by the treating physician based on clinical needs for the benefit of the patient, rather than for the purposes of the study.
- The patient had been treated with another antipsychotic for at least 4 months after remission of a schizophrenia relapse.

Group 2

- The patient began treatment with intramuscular PP1M no more than 7 days prior, or the treating physician made a clinical decision to prescribe PP1M at any dose based on the patient's clinical needs.
- The patient had been treated with another antipsychotic for at least 4 months after remission of a schizophrenia relapse. Before inclusion in the second group, the patient had undergone an initial course of OP or risperidone of any duration but not less than 3 days.

Group 3

- The patient began treatment with intramuscular PP3M no more than 7 days prior, or the treating physician made a clinical decision to prescribe PP3M at any dose based on the patient's clinical needs.
- The patient had been treated with PP1M for at least 4 months after remission of a schizophrenia relapse.

Exclusion criteria:

All participants

- The presence of any other mental disorder diagnosis, aside from paranoid schizophrenia.
- Refusal of the patient to participate in the observation and/or assessment of his/her mental state using clinical psychometric scales.
- Participation of the patient in any other clinical or observational drug study or other treatment methods.
- Contraindications to paliperidone, determined by the treating physician based on the clinical presentation of the disease, existing comorbidities, and other individual risks, as well as contraindications specified in the instruction for the use of paliperidone, approved by the Ministry of Health of the Russian Federation.
- Presence of clinically significant somatic diseases such as kidney, liver, cardiovascular, respiratory system disorders, cerebrovascular diseases in a decompensated stage, cancer and other progressive diseases, for which paliperidone is contraindicated.
- A history of severe drug allergies or hypersensitivity to paliperidone, risperidone, or their components, or allergy to three or more different medications.
- Other contraindications to the use of paliperidone, as determined by the instructions for use or the physician's judgment.

A patient was excluded from the program in the following cases:

- Withdrawal of informed consent, refusal to take the medications prescribed as part of the program, or refusal to undergo the procedures of the observational program.
- The need to discontinue paliperidone due to side effects, the risk of worsening of physical illness, or worsening of mental health.
- If, in the physician's opinion, there was a need to change the therapy regimen, such as replacing antipsychotics or prescribing a second antipsychotic with a marked selective antipsychotic effect.
- Any other situation where discontinuation, change of therapy, or the decision to end the observation was made by the treating physician or the patient in their best interest.
- Other circumstances that prevented proper treatment and observation of the patient.

The patients, whose mental state was the subject of monitoring, were divided into three observation groups: 1) those receiving OP; 2) those receiving the injectable PP1M; and 3) those receiving the injectable PP3M. Since the patients experienced individually expressed symptoms, course, and history of schizophrenia, concomitant therapy (mood stabilizers, antidepressants, tranquilizers, and other drugs with predominantly sedative effects, as well as medications to manage neurological symptoms) was allowed. This therapy was prescribed by the treating physician based on clinical indications, such as existing affective disorders, sleep disturbances, and the side effects of psychopharmacotherapy. The prescription, discontinuation, selection, and dose adjustment of all paliperidone dosage forms and other concomitant medications were made based on the indications for these medications, the recommended doses in the instructions for usage, the clinical need, and the interests of the patients, rather than the objectives of the study.

The observational program included 155 patients, who either had completed the observation program or had withdrawn for various reasons (Table 1).

A qualitative determination of psychopathological manifestations and an ordinal assessment of symptom severity were conducted at baseline, before the start of treatment, on Day 1 (Visit 1), and subsequently on days 90 (Visit 2), 180 (Visit 3), 270 (Visit 4), and 360 (Visit 5) of outpatient treatment, with an acceptable interval of ±7 days. Thus, the maximum duration of the observation period for each patient was 360 days (52 weeks or 12 months).

Data sources

The main data collection method was a clinical-descriptive approach, which involved studying the patient's history, identifying complaints about health, observing patient's mental and physical condition over time, and examining

the specifics of social functioning. For the study, a case report form was developed, which included anonymized data on age, diagnosis, concomitant therapy, presence or absence of treatment-related AEs, predominant symptoms, and their severity. The start and end times of the study were recorded, along with the reasons for termination.

Measurements

To quantitatively assess the dynamics of various clinical manifestations of schizophrenia and the quality of social functioning, at all visits the following scales were used:

1. PSP scale, developed as a result of the integration of the Diagnostic and Statistical Manual of Mental Disorders 4th revision (DSM-IV) Social and Occupational Functioning Assessment Scale (SOFAS) and the Global Assessment Functioning (GAF) scale. The PSP is a scale with a maximum score of one hundred points, divided into 10 equal intervals with ordinal designations [57]. The assessment takes into account four categories of functioning: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behavior. The scale has proven to be a reliable and quick tool for measuring personal and social functioning, with several advantages compared to other tools [57–61].
2. The DSM-5 Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS) scale, which allows the clinician to quantitatively assess the severity of core psychotic symptoms, including disorganized speech, delusions, hallucinations, abnormal psychomotor behavior, negative symptoms, as well as cognitive impairments, depression, and mania — a total of 8 items. The severity of psychotic symptoms is rated on a 5-point scale from 0 (symptom absent) to 4 (symptom present and significantly pronounced), based on the clinician's judgment, and it can be completed during a routine clinical examination. The clinician is asked to rate the severity of each symptom the patient experienced over the past seven days [62–65]. Despite the controversial and even critical assessments of the CRDPSS consistency, convergent validity, and inter-rater reliability [66, 67],

Table 1. Characteristics of study groups

Variables	OP (*n*=54) f(%)	PP1M (*n*=50) f(%)	PP3M (*n*=51) f(%)	Total (*n*=155) f(%)	Statistical analysis
					χ^2-test
Male Female	25 (46.3) 29 (53.7)	24 (48.0) 26 (52.0)	24 (47.1) 27 (52.9)	73 (47.1) 82 (52.9)	χ^2=0.030; df=2; *p*=0.985
Diagnosis F20.00 F20.01 F20.03 F20.09	11 (20.4%) 20 (37.0%) 12 (22.2%) 11 (20.4%)	8 (16.0%) 33 (66.0%) 2 (4.0%) 7 (14.0%)	16 (31.4%) 31 (60.8%) 3 (5.9%) 1 (2.0%)	35 (22.6%) 84 (54.2%) 17 (11.0%) 19 (12.3%)	χ^2=24.536; df=6; *p*=0.000319
					One-way ANOVA
Age Mean (SD)	36.1 (10.2)	38.4 (9.41)	38.6 (9.22)	37.7 (9.64)	OP vs PP1M: MD=-2.31; t=-1.22; df=152; *p*=0.443 OP vs PP3M: MD=-2.534; t=-1.348; df=152; *p*=0.371 PP1M vs PP3M: MD=-0.228; t=-0.119; df=152; *p*=0.992
Duration of schizophrenia Mean (SD)	11.24 (9.05)	13.42 (8.67)	12.52 (8.22)	12.36 (8.7)	OP vs PP1M: MD=2.18; t=1.28; df=152; *p*=0.407 OP vs PP3M: MD=-1.289; t=-1.28; df=152; *p*=0.727 PP1M vs PP3M: MD=0.891; t=0.517; df=152; *p*=0.863
Number of hospitalizations Mean (SD)	3.65 (4.05)	4.50 (4.03)	5.08 (4.75)	4.39 (4.30)	OP vs PP1M: MD=-0.852; t=-1.01; df=152; *p*=0.570 OP vs PP3M: MD=-1.430; t=-1.709; df=152; *p*=0.205 PP1M vs PP3M: MD=-0.578; t=-0.678; df=152; *p*=0.777

Note: n — the number of patients in the sample; f(%) — frequency and percentage; SD — the standard deviation, MD — the mean difference; df — the degrees of freedom; χ^2 — the value of the Pearson chi-squared test; t — the t-test; *p* — the significance level (*p*-value); OP — oral paliperidone; PP1M — paliperidone palmitate once a month; PP3M — paliperidone palmitate once every three months; ANOVA — one-way analysis of variance.

we attempted to apply it, as it remains an accessible tool in general practice based on clinical examination and can be useful in gauging the severity of different schizophrenia symptoms and predicting the course of the psychosis [68].

3. The Symptoms Qualifier Scales (SQS) from ICD-11, which include six other sections (domains) of mental disorders that are commonly observed in individuals with primary psychotic disorders: positive symptoms, negative symptoms, depressive symptoms, manic symptoms, psychomotor symptoms, and cognitive symptoms. These sections "were selected by the ICD-11 Working Group on Schizophrenia and Other Primary Psychotic Disorders through a careful review of the literature and the scientific validation process. Indeed, these areas align well with the general consensus on important areas of schizophrenia and other psychotic disorders" [65, 69]. Each of the domains can be rated on a 4-point scale, from 0 (symptom absent) to 3 (symptom present and significantly pronounced).
4. CGI-S scale, which allows for a general assessment of the severity of the mental disorder based on the physician's clinical opinion [70–74].
5. The 4-Items Negative Symptoms Assessment (NSA-4) scale consists of four items, each rated on a scale from 0 to 4. The scale is an abridged and adapted version for broader clinical use of the NSA-16 (16-Items Negative Symptoms Assessment) scale, which includes four items selected verbatim: restricted speech quantity, reduced emotion, reduced social drive, and reduced interests, as well as an overall summary rating. Each of the four items and the total negative symptoms are scored on a scale from 1 to 6, where "1" indicates no reduction compared to normal behavior, and "6" indicates a significant reduction or absence of behavior with severe functional impairment [75].

The primary effectiveness measure in the observational program was a statistically significant increase in the final mean score on the PSP scale, with a final score increase of at least 10.7 points (17.1%), which corresponds to the minimal detectable change calculated for it [60]. Additional effectiveness measures included a reduction in the manifestations of schizophrenia and, specifically, a statistically significant decrease in the scores of individual items of the dimensional assessments on CRDPSS and SQS, the mean CGI-S score, and the mean total score on the NSA-4 scale. The time to premature study discontinuation in the 3 compared groups was used as an exploratory parameter.

Statistical analysis

The general characteristics of the population were presented using descriptive statistical methods, with continuous data expressed as means and standard deviations (SD), medians, and the first and third quartiles (Q1 and Q3). Comparisons of interval values were made using one-way analysis of variance (ANOVA), with a Tukey adjustment for multiple comparisons. Categorical data were presented as absolute and relative frequencies. The comparison of the baseline values of the representation of different clinical variants of schizophrenia and psychopathological syndromes in independent samples was conducted using Pearson's chi-squared test.

Primary and secondary parameters were studied in a separate repeated measures ANOVA model with a fixed group factor and an assessment of between-group contrasts based on changes in scores on the respective scales between visit 1 and visits 2, 3, 4, and 5.

Analysis of differences in the time to premature study discontinuation was conducted using Kaplan-Meier survival curves, with the differences between the groups compared using the Log-rank test, which calculates the mean duration of participation in the study for each group and the relative risk in case of full study completion.

All types of analyses were conducted using the software products jamovi v. 2.3 (The jamovi project, 2022) and IBM SPSS Statistics 26.

RESULTS

Participants

The analysis included 155 patients, who either completed the observation program or withdrew for various reasons.

Descriptive statistics for the overall sample are presented in Table 1. The total sample consisted of 54 patients receiving OP, 50 patients receiving PP1M intramuscular injections, and 51 patients receiving PP3M intramuscular injections.

Patients receiving different dosage forms of paliperidone did not show significant differences in terms of sex, age, disease duration, and number of hospitalizations.

A total of 155 patients were diagnosed with paranoid schizophrenia. Cases with a diagnosed episodic (recurrent) course (F20.03) were the most common and patients with an episodic course with progressive deficit (F20.01) were the fewest in the OP group, compared to other groups.

Table 2. Study completions and early withdrawals

	OP (*n*=54) f(%)	PP1M (*n*=50) f(%)	PP3M (*n*=51) f(%)	Total (*n*=155) f(%)	Statistical analysis χ^2; df; *p*-value
Result of study					
Completed Withdrew	11 (20.4) 43 (79.6)	24 (48.0%) 26 (52.0)	30 (58.8%) 21 (41.2)	65 (41.9) 90 (58.1)	χ^2=17.042; df=2; *p*=0.000179
Reasons for withdrawal					
lack of efficacy	10 (18.5%)	10 (20.0%)	12 (23.5%)	32 (20.7%)	χ^2=19.356; df=8; *p*=0.010796
AE	7 (13.0%)	3 (6.0%)	4 (7.9%)	14 (9.0)	
non-compliance	6 (11.1%)	–	–	6 (3.9%)	
Switching to another dosage form	18 (33.3%)	12 (24.0%)	2 (3.9%)	32 (20.7%)	
unknown reasons	2 (3.7%)	1 (2.0%)	3 (5.9%)	6 (0.11%)	

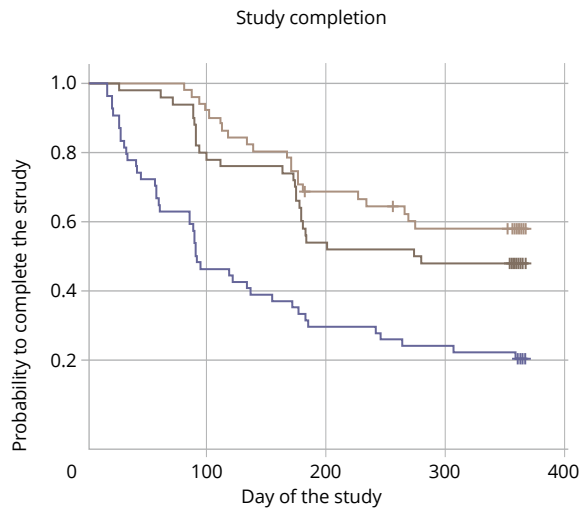
Note: n — the number of patients in the sample; f(%) — frequency and percentage; df — the degrees of freedom; χ^2 —the value of the Pearson chi-squared test; *p* — the significance level (*p*-value); OP — oral paliperidone; PP1M — paliperidone palmitate once a month; PP3M — paliperidone palmitate once every three months; AE — adverse effect.

Patients with an episodic course with progressive deficit (F20.09) were more common in the PP1M group. In the PP3M group, patients with a continuous course (F20.00) were more common than in other groups and fewer patients had a recurrent course (F20.03) or a short observation period (less than one year) (F20.09) compared to the OP group. The opposite ratios of patients with episodic and continuous courses of schizophrenia in the OP and PP3M groups likely contributed to the fact that, at baseline visit, the dimension "hallucinations" was higher in the OP group, while the dimension "negative symptoms" and the total score on the NSA-4 scale were higher in the PP3M group. However, the baseline values of the clinically similar domains "Positive symptoms" and "Negative symptoms" on the SQS (ICD-11) scale did not show significant differences across the groups (Table S1 in the Supplementary).

Analysis of treatment duration and patients withdrawal

Table 2 presents data on the number of patients who completed all visits and withdrew from observation and the reasons for premature withdrawal of patients receiving different dosage forms of paliperidone. In the PP1M and PP3M groups, the numbers were approximately the same: about half of the patients completed all visits and completed observation, while in the OP group, significantly fewer patients completed the study. Withdrawal of a third of patients receiving OP treatment and a quarter of patients receiving PP1M is explained by their switching to more long-acting dosage forms of paliperidone — PP1M and PP3M, respectively. This decision was made by the physician in accordance with the protocol of this observational study and in the interests of successful treatment of the patient. In the PP3M group, two cases of return to PP1M treatment were associated with the lack of free access to the drug at the required time. Discontinuation of observation due to relapses of schizophrenia or insufficient efficacy of paliperidone was observed in all groups with approximately identical frequency of about 20%. Cases of non-compliance with the prescribed therapy or refusal to continue treatment were reported only in the OP group. Also, in all groups, in isolated cases, patients mixed the next visit, and it was impossible to determine the reasons behind their refusal to participate in the observation.

Analysis of the time to completion of participation in the observation (Figure 1) demonstrated that in the PP1M and PP3M groups, a greater proportion of patients fully completed the study program (*n*=24, 48,0% and *n*=30, 58,8%, respectively) compared to the OP group (*n*=11, 20,4%). The mean survival time in the OP group was 154.926 days (95% CI: 120.270–189.582), while in the PP1M group, it was 250.320 days (216.884–283.756), and in the PP3M group, it was 281.618 days (251.848–311.388). Testing for equality of survival distributions among the three groups showed statistically significant differences (χ^2=28.381, df=2, *p*=0.0001, Log-Rank test). Early withdrawal from the study in the OP group was mainly due to a switch by patients in this group to another dosage form of paliperidone, which was based on the patient's interests; i.e., either at the patient's request or for clinical reasons. Despite



	Day				
Group	**0**	**100**	**200**	**300**	**400**
OP	54	40	27	16	14
PP1M	50	42	35	28	25
PP3M	51	46	38	33	31

Figure 1. Kaplan-Meier curves of the probability of completing the study for patients from the OP, PP1M, and PP3M groups.

Note: OP — oral paliperidone; PP1M — paliperidone palmitate once a month; PP3M — paliperidone palmitate once every three months.

Source: Reznik et al., 2024

the seemingly higher number of patients completing the full observation program and a somewhat higher mean survival time in the PP3M group compared to the PP1M group, the Log-rank test did not show significant differences (χ^2=1.292, df=1, p=0.256).

Dynamics of symptoms and social functioning

At the baseline visit, there were no significant differences in the scores of the SQS Positive, Negative, and Depressive symptom domains, as well as in the "Hallucinations", "Delusions", "Negative Symptoms", and "Depressive Symptoms" scales from the dimensional assessment of the CRDPSS. The mean CGI-S, NSA-4, and PSP scores likewise did not show significant differences across the 3 groups (Table S2, Table S3 and Table S4 in the Supplementary).

The two-way repeated-measures ANOVA conducted across the entire sample of patients receiving paliperidone demonstrated a consistent and statistically significant reduction in the severity of negative and depressive symptoms as measured by the SQS (Table 3, Figure 2A, B), the hallucinations, delusions, negative symptoms, and depressive symptoms as assessed by the CRDPSS (Table 4, Figures 3), negative symptoms according to NSA-4 (Table 5 and Figure 4), and the overall severity of schizophrenia on the CGI-S scale (Table 5 and Figure 5).

A more detailed analysis revealed a significant reduction in the SQS positive symptoms domain compared to the baseline in the overall sample by visit 4 (t=3.976; p <0.001; p_{tukey}=0.002), but this parameter subsequently returned to its baseline levels. However, in the individual comparison groups (OP, PP1M, and PP3M), no significant differences in positive symptoms were found either across the groups or visits. A reduction in the severity of negative symptoms was observed as early as at visit 2 (t=3.658; p <0.001; p_{tukey}=0.005) and remained throughout subsequent visits. Significant differences were identified only in the PP1M group between visits 1 and 3 (t=3.942; p <0.001; p_{tukey}=0.015), while no statistically significant differences were observed between the groups at any visit. Depressive symptoms on the SQS had improved by visit 2 (t=3.278; p=0.002; p_{tukey}=0.014), with significant differences from the baseline remaining throughout all subsequent visits. However, no significant differences were observed either between the comparison cohorts or across visits within them.

In the CRDPSS domains for the entire patient sample, a significant reduction from the baseline was achieved in "hallucinations" by visit 2 (t=4.228; p <0.001; p_{tukey} <0.001) and was maintained throughout subsequent visits. However, a slight increase in hallucinations was noted in the OP cohort between visits 4 and 5 (Figure 3A). Significant improvement in the "delusions" domain of the CRDPSS from

Table 3. Changes in three Symptoms Qualifier Scales domain scores (positive, negative and depressive symptoms) with statistically significant differences*

	Source of variation	Sum of Squares	df	Mean Square	F	*p*	η^2	η^2_p
Positive symptoms	Visit	2.54	4	0.634	5.58	<0.001	0.024	0.083
	Visit × Dosage form	1.55	8	0.194	1.71	0.098	0.015	0.052
	Residual	28.16	248	0.114	-	-	-	-
	Dosage form	5.33	2	2.67	2.43	0.098	0.051	0.073
	Residual	67.92	62	1.10	-	-	-	-
Negative symptoms	Visit	3.19	4	0.797	7.33	<0 .001	0.039	0.106
	Visit × Dosage form	1.65	8	0.206	1.84	0.070	0.020	0.056
	Residual	27.72	248	0.112	-	-	-	-
	Dosage form	0.512	2	0.256	0.311	0.734	0.006	0.010
	Residual	51.131	62	0.825	-	-	-	-
Depressive symptoms	Visit	7.63	4	1.908	10.933	<0.001	0.071	0.133
	Visit × Dosage form	1.26	8	0.157	0.901	0.516	0.012	0.025
	Residual	49.57	248	0.175	-	-	-	-
	Dosage form	4.87	2	2.437	3.93	0.024	0.045	0.100
	Residual	44.06	62	0.621	-	-	-	-

Note: df — the degrees of freedom; *p* — the significance level (p-value); η^2 — effect size measure; η^2p — adjusted effect size indicator; *Two-way Repeated-measures ANOVA results.

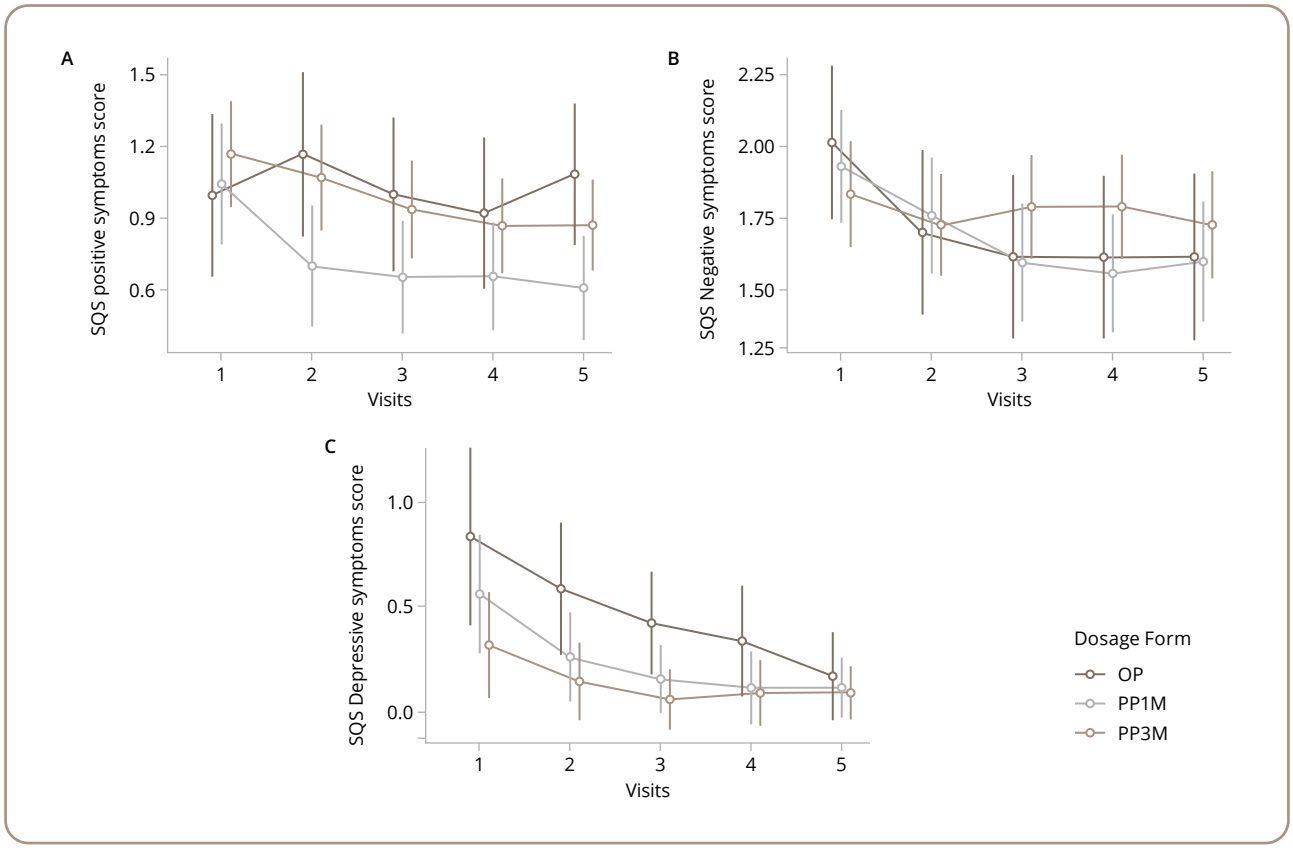


Figure 2. Dynamics of Symptoms Qualifier Scales scores in the paliperidone groups.

Note: SQS — the Symptoms Qualifier Scales; OP — oral paliperidone; PP1M — paliperidone palmitate once a month; PP3M — paliperidone palmitate once every three months.

Source: Reznik et al., 2024

Table 4. Changes in the DSM-5 Clinician-Rated Dimensions of Psychosis Symptom Severity dimension scores with statistically significant differences across the visits or study groups*

	Source of variation	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
Hallucinations	Visit	14.39	4	3.597	14.33	<0.001	0.093	0.188
	Visit × Dosage form	4.19	8	0.524	2.09	0.038	0.027	0.063
	Residual	62.23	248	0.251	-	-	-	-
	Dosage form	0.328	2	0.164	0.138	0.872	0.002	0.002
	Residual	73.961	62	1.193	-	-	-	-
Delusions	Visit	5.54	4	1.386	8.20	<0.001	0.025	0.117
	Visit × Dosage form	1.79	8	0.224	1.32	0.232	0.008	0.041
	Residual	41.92	248	0.169	-	-	-	-
	Dosage form	15.3	2	7.65	3.08	0.053	0.070	0.090
	Residual	153.9	62	2.48	-	-	-	-
Disorganized speech	Visit	7.76	4	1.941	9.87	<0.001	0.049	0.472
	Visit × Group	3.27	8	0.408	2.08	0.039	0.021	0.244
	Residual	48.75	248	0.197	-	-	-	-
	Group	1.56	2	0.781	0.483	0.619	0.010	0.010
	Residual	100.33	62	1.618	-	-	-	-
Negative symptoms	Visit	22.38	4	5.596	26.56	<0.001	0.134	0.300
	Visit × Dosage form	1.93	8	0.241	1.14	0.335	0.011	0.036
	Residual	52.25	248	0.211	-	-	-	-
	Dosage form	13.9	2	6.96	5.59	0.006	0.083	0.153
	Residual	77.2	62	1.24	-	-	-	-
Cognitive symptoms	Visit	3.68	4	0.920	5.92	<0.001	0.030	0.028
	Visit × Group	2.01	8	0.251	1.61	0.121	0.017	0.015
	Residual	38.53	248	0.155	-	-	-	-
	Group	7.84	2	3.92	3.07	0.053	0.062	0.060
	Residual	79.16	62	1.28	-	-	-	-
Psychomotor symptoms	Visit	10.57	4	2.642	12.48	<0.001	0.082	0.079
	Visit × Group	4.63	8	0.579	2.74	0.007	0.038	0.035
	Residual	52.49	248	0.212	-	-	-	-
	Group	0.285	2	0.142	0.133	0.876	0.002	0.002
	Residual	66.312	62	1.070	-	-	-	-
Depressive symptoms	Visit	17.08	4	4.271	10.752	<0.001	0.079	0.148
	Visit × Group	2.34	8	0.293	0.737	0.658	0.011	0.023
	Residual	98.51	248	0.397	10.752	-	-	-
	Group	8.55	2	4.27	2.91	0.062	0.039	0.086
	Residual	90.94	62	1.47	-	-	-	-
Manic symptoms	Visit	0.298	4	0.0746	2.10	0.082	0.015	0.014
	Visit × Group	0.609	8	0.0761	2.14	0.033	0.029	0.029
	Residual	8.825	248	0.0356	-	-	-	-
	Group	0.340	2	0.170	0.935	0.398	0.017	0.016
	Residual	11.272	62	0.182	-	-	-	-

Note: df — the degrees of freedom; *p* — the significance level (p-value); η^2 — effect size measure; η^2p — adjusted effect size indicator; *Two-way Repeated-measures ANOVA results.

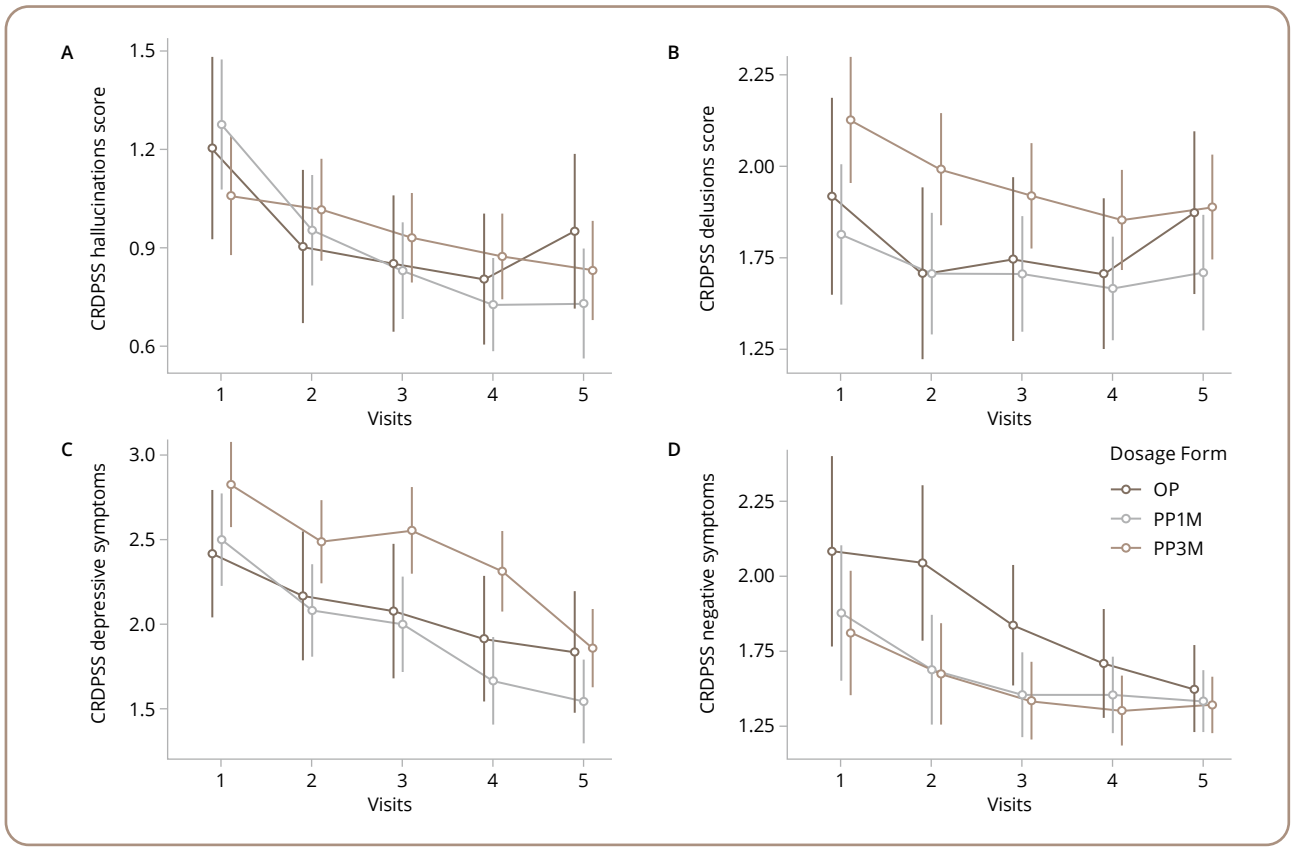


Figure 3. Dynamics of Clinician-Rated Dimensions of Psychosis Symptom Severity scale scores in the paliperidone groups.

Note: CRDPSS — Clinician-Rated Dimensions of Psychosis Symptom Severity scale; OP — oral paliperidone; PP1M — paliperidone palmitate once a month; PP3M — paliperidone palmitate once every three months.

Source: Reznik et al., 2024

Table 5.Changes in the Clinical Global Impression scale, 4-Items Negative Symptoms Assessment scale and the Personal and Social Performance scale scores with statistically significant differences between the visits or study groups*

	Source of variation	Sum of Squares	df	Mean Square	F	*p*	η^2	η^2_p
CGI-S	Visit	8.89	4	2.223	16.05	<0.001	0.082	0.206
	Visit × Group	1.63	8	0.203	1.47	0.170	0.015	0.045
	Residual	34.36	248	0.139	-	-	-	-
	Group	7.70	2	3.850	4.31	0.018	0.071	0.122
	Residual	55.33	62	0.892	-	-	-	-
NSA-4	Visit	1206.3	4	301.57	59.406	<0.001	0.028	0.489
	Visit × Group	26.5	8	3.32	0.653	0.732	0.005	0.021
	Residual	1258.9	248	5.08	-	-	-	-
	Group	480	2	240.0	5.25	0.008	0.083	0.145
	Residual	2835	62	45.7	-	-	-	-
PSP	Visit	6903	4	1725.9	52.48	<0.001	0.170	0.458
	Visit × Group	706	8	88.3	2.68	0.008	0.017	0.080
	Residual	8156	248	32.9	-	-	-	-
	Group	2690	2	1345	3.77	0.028	0.066	0.109
	Residual	22103	62	357	-	-	-	-

Note: df — the degrees of freedom; *p* — the significance level (p-value); η^2 — effect size measure; η^2p — adjusted effect size indicator; CGI-S — the Clinical Global Impression scale; NSA-4 — the 4-Items Negative Symptoms Assessment scale; PSP — the Personal and Social Performance scale; *Two-way Repeated-measures ANOVA results.

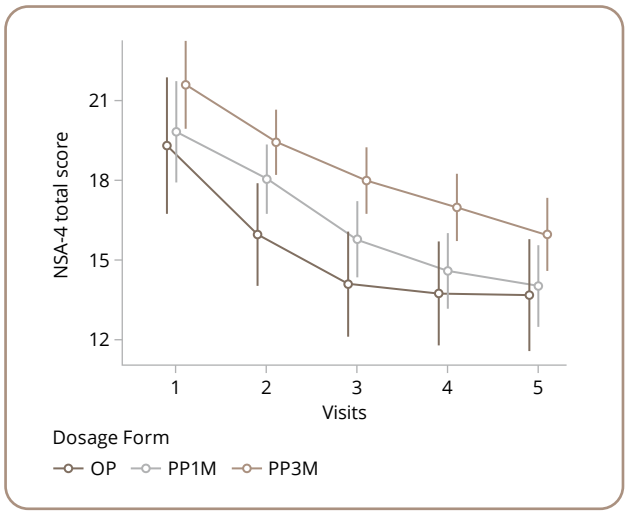


Figure 4. Dynamics of the mean NSA-4 total scores in the paliperidone groups.

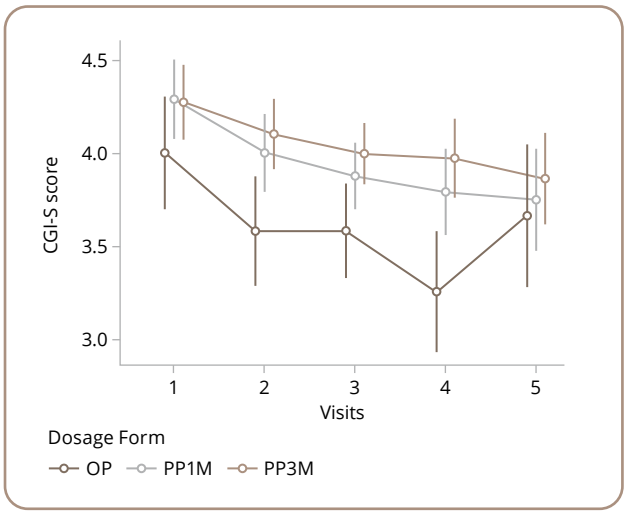


Figure 5. Dynamics of the mean CGI-S scores in the paliperidone groups.

Note: NSA-4 — the 4-Items Negative Symptoms Assessment scale; CGI-S — the Clinical Global Impression scale; OP — oral paliperidone; OP — oral paliperidone; PP1M — paliperidone palmitate once a month; PP3M — paliperidone palmitate once every three months.

Source: Reznik et al., 2024

the baseline was also achieved by visit 2 (t=4.111; p <0.001; p_{tukey} <0.001) and was maintained across all visits. In this domain, there was a worsening of the state of delusion compared to baseline levels in the OP group at the final visit (Figure 3B), which noticeably affected the overall result, leading to no significant differences between visits 1 and 5. A more pronounced, gradual improvement was observed in the "negative symptoms" domain. Statistically significant differences were noted by visit 2 (t=4.018; p <0.001; p_{tukey}=0.001), with a significant positive trend maintained across all subsequent assessments. In the comparison cohorts, significant differences were detected only at visit 3 between the PP1M and PP3M groups (t=3.739; p <0.001; p_{tukey}=0.030). In the CRDPSS "depressive symptoms" domain, significant differences for the entire sample emerged by visit 3 (t=3.459; p <0.001; p_{tukey}=0.008) and remained throughout the study. However, in individual comparison cohorts, no significant differences were identified between the visits or across the groups after Tukey's adjustment.

Post-hoc comparisons of the CGI-S and NSA-4 scales across the entire sample of patients receiving paliperidone confirmed a statistically significant reduction in disease severity, based on the clinician's global assessment, and a decrease in the severity of negative symptoms by visit 2 (t=4.639; p <0.001; p_{tukey} <0.001 and t=4.68; p <0.001; p_{tukey} <0.001, respectively), with sustained positive dynamics throughout the observation period (Figures 4 and 5). However, among patients taking different dosage forms of paliperidone, significant changes in CGI-S compared to the baseline were observed only in the OP group at visit 4 (t=4.523; p <0.001; p_{tukey}=0.002), in the PP1M group starting from visit 3 (t=4.2147; p <0.001; p_{tukey}=0.007) and continuing until the end of the observation period, while no significant changes were detected in the PP3M group. Intergroup differences were identified only between the OP and PP3M groups and only at visit 4 (t=3.749; p < 0.001; p_{tukey} <0.027). The CGI-S scale, which provides a global synthetic impression of disease severity, primarily reflects the clinician's assessment of the psychotic symptom severity and, therefore, in our observations it assumes a generally flat character, similar to the dynamics of positive symptoms on the SQS scale. The dynamics of negative symptoms on the NSA-4 scale were more pronounced across all three comparison groups, with significant differences observed at visit 3 (OP group: p_{tukey}=0.003; PP1M and PP3M groups: p_{tukey} <0.001) and maintained across all subsequent assessments. Notably, the NSA-4 variance is generally similar to the dynamics of the CRDPSS negative symptom domain (Figures 3D and 4).

The assessment of social and personal functioning using the PSP scale in the overall sample treated with all dosage forms of paliperidone showed improvement (Table 5, Figure 6), with statistically significant differences achieved as early as visit 2 (t=5.24; p <0.001; p_{tukey} <0.001) and a steady

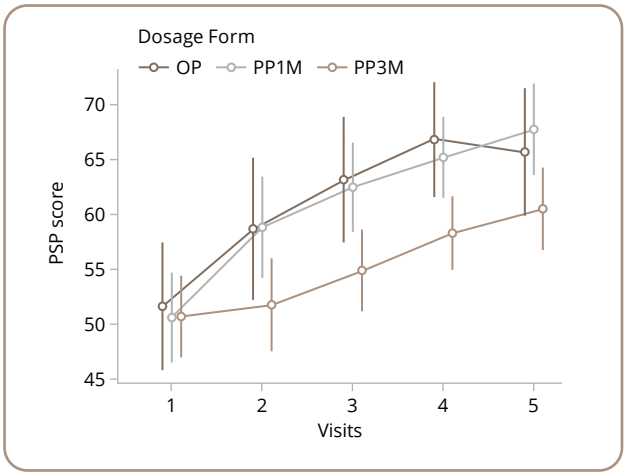


Figure 6. Dynamics of the mean PSP total scores in the paliperidone groups.

Note: PSP — the Personal and Social Performance scale; OP — oral paliperidone; PP1M — paliperidone palmitate once a month; PP3M — paliperidone palmitate once every three months.

Source: Reznik et al., 2024

improvement observed at subsequent visits. A significant overall intergroup difference was found between patients receiving PP1M and PP3M (t=2.4508; p=0.017; p_{tukey}=0.044), although no differences were detected at individual visits. In the OP group, the mean PSP score increased by more than 17.2% from the baseline value (49.2) to visit 3 (62.5) and by 34% by the end of the observation period (65.8). In the PP1M group, the mean PSP score similarly increased by about 17.2% from the baseline value (50.8) to visit 3 (59.6) and by 34% (65.8) by the end of the observation period. In the PP3M group, the mean PSP score increased by more than 17.2% ultimately by the final visit reaching 60.5 points.

Tolerability analysis

A total of 88 patients (56.8%) reported experiencing AEs. AEs were reported by 35 patients (64.8%) in the OP group, 25 patients (50%) in the PP1M group, and 26 patients (51.0%) in the PP3M group. The full list of AEs is presented in Table 6. In the OP group, eight AEs occurred in >5.5% of the patients: weight gain, in six patients (11.1%); increased appetite, in five (9.3%); akathisia, in five (9.3%); hyperprolactinemia, in five (9.3%); irregular menstrual cycles, in five (9.3%); COVID-19, in four (7.4%); reduced attention, in four (7.4%); and anxiety, in four (7.4%). Other AEs were reported as isolated cases. In the PP1M group, 10 AEs occurred in >5.5% of the patients: COVID-19, in five patients (10.0%); hyperprolactinemia, in five (10.0%); reduced attention, in four (8.0%); akathisia, in three (6.0%); irregular menstrual cycle, in three (6.0%); weight gain, in three (6.0%); increased appetite, in three (6.0%); headaches, in three (6.0%); drowsiness, in three (6.0%); and anxiety, in three (6.0%). In the PP3M group, 11 AEs occurred in >5.5% of the patients: hyperprolactinemia, in six patients (11.8%); weight gain, in five (9.8%); COVID-19, in five (9.8%); tremor, in five (9.8%); akathisia, in four (7.8%); irregular menstrual cycles, in four (7.8%); increased appetite, in four (7.8%); dizziness, in four (7.8%); insomnia, in four (7.8%); tachycardia, in three (5.9%); and reduced attention, in three (5.9%). Although no statistically significant differences were found (Table 7), likely due to the sample size, it is noteworthy that extrapyramidal symptoms, including newly identified cases, were slightly more frequent in the OP group (Table 8). Overall, the profile of AEs was similar to and typical of paliperidone. Across all three cohorts, the most common AEs were mild extrapyramidal symptoms (akathisia and tremor, which had minimal impact on the patients' overall condition), hyperprolactinemia and its clinical manifestations, increased appetite, weight gain, and a situational AE of COVID-19, which proved generally mild and not considered a serious AE, except in one case where it was led the physician to discontinue therapy.

DISCUSSION

An observational study was conducted to evaluate the clinical dynamics and social functioning ability of patients with schizophrenia undergoing therapy with three dosage forms of paliperidone: OP, PP1M, and PP3M.

In the OP group, compared to the other groups, the cases with a diagnosed episodic (recurrent) course (F20.03) — the most favorable course in schizophrenia — were significantly more common and patients with an episodic course with progressive deficit (F20.01) were the fewest. Patients with an episodic course with progressive deficit (F20.09) were significantly more common in the PP1M group. In the PP3M group, patients with a continuous course (F20.00) were significantly more common than in the other groups (p <0.05), and fewer patients had a recurrent course (F20.03) or a short observation period (less than one year) (F20.09) compared to the OP group. This likely explains the higher baseline values for the "Hallucinations" dimension of the CRDPSS in the OP group and the more pronounced negative symptoms on the CRDPSS and NSA-4 scales in the PP3M group. Overall, these patterns reflect the continued practice of prescribing long-acting formulations of paliperidone to patients with a long-term

Table 6. List and frequency of adverse effects observed in the study

Adverse effects	All patients (*n*=155)		OP (*n*=54)		PP1M (*n*=50)		PP3M (*n*=51)	
	f	%	f	%	f	%	f	%
Any AE	88	56.8	35	64.8	25	50.0	26	51.0
Registered EPS	28	18.1	12	22.2	8	16.0	8	15.7
Newly identified EPS	16	10.3	7	13.0	4	8.0	4	7.8
Akathisia	23	14.8	9	16.7	6	12.0	8	15.7
New akathisia	12	7.7	5	9.3	3	6.0	4	7.8
Acute dystonia	2	1.3	1	1.9	1	2.0	-	-
Hypokinesia	4	2.6	2	3.7	1	2.0	1	2.0
New hypokinesia	2	1.3	1	1.9	-	-	1	2.0
Tremor	16	10.3	7	13.0	4	8.0	5	9.8
New tremor	7	4.5	3	5.6	2	4.0	2	3.9
Hypersalivation	3	1.9	1	1.9	1	2.0	1	2.0
New hypersalivation	1	0.7	-	-	-	-	1	2.0
Tardive dyskinesia	1	0.7	-	-	-	-	1	2.0
New tardive dyskinesia	-	-	-	-	-	-	-	-
Hyperprolactinemia	16	10.3	5	9.3	5	10.0	6	11.8
Gynecomastia	6	3.9	2	3.7	2	4.0	2	3.9
Galactorrhea	5	3.2	2	3.7	1	2.0	2	3.9
Irregular menstrual cycle	12	7.7	5	9.3	3	6.0	4	7.8
Weight gain	15	9.7	6	11.1	3	6.0	5	9.8
Weight loss	3	1.9	1	1.9	-	-	2	3.9
Diarrhea	3	1.9	2	3.7	-	-	1	2.0
Nausea	6	3.9	3	5.6	1	2.0	2	3.9
Increased appetite	12	7.7	5	9.3	3	6.0	4	7.8
Decreased appetite	5	3.2	2	3.7	1	2.0	2	3.9
Hyperglycemia	2	1.3	-	-	-	-	2	3.9
Bradycardia	4	2.6	-	-	2	4.0	2	3.9
Increased blood pressure	2	1.3	1	1.9	-	-	1	2.0
Tachycardia	7	4.5	3	5.6	1	2.0	3	5.9
Rash	1	0.7	1	1.9	-	-	-	-
COVID-19	14	9.0	4	7.4	5	10.0	5	9.8
Dizziness	6	3.9	1	1.9	1	2.0	4	7.8
Headache	7	4.5	3	5.6	3	6.0	1	2.0
Decreased attention	11	7.1	4	7.4	4	8.0	3	5.9
Somnolence	7	4.5	3	5.6	3	6.0	1	2.0
Insomnia	9	5.8	3	5.6	2	4.0	4	7.8
Anxiety	8	5.2	4	7.4	3	6.0	1	2.0

Note: f(%) — frequency and percentage; EPS — extrapyramidal symptoms ; AE — adverse effects; OP — oral paliperidone; PP1M — paliperidone palmitate once a month; PP3M — paliperidone palmitate once every three months.

Table 7. Frequency of adverse effects in paliperidone groups

Group	Adverse effects		Statistical analysis χ^2; df; *p*-value
	f	%	
OP (*n*=54)	35	64.8	χ^2=2.931; df=2; *p*=0.249
PP1M (*n*=50)	25	50.0	
PP3M (*n*=51)	26	51.0	

Table 8. Extrapyramidal symptoms in paliperidone groups

Group	Adverse effects		Statistical analysis χ^2; df; *p*-value
	f	%	
OP (*n*=54)	12	22.2	χ^2=2.991; df=2; *p*=0.236
PP1M (*n*=50)	8	16.0	
PP3M (*n*=51)	8	15.7	

Note: n — the number of patients in the sample, f(%) — frequency and percentage; df — the degrees of freedom; χ^2 —the value of the Pearson chi-squared test; *p* — the significance level (*p*-value); OP — oral paliperidone; PP1M — paliperidone palmitate once a month; PP3M — paliperidone palmitate once every three months.

and continuous disorder, who are typically characterized by poorer adherence to prescribed therapy, often poor social support in their efforts to adhere to uninterrupted treatment, and, at the same time, milder exacerbations. It is important to note that in patients with prolonged and continuous schizophrenia, exacerbations tend to be less acute. Symptoms such as agitation, mania, negativism, hostility, and aggression are less pronounced than in the early stages of the disease or in cases with an episodic course. Such deteriorations are often less acute than in periodic forms of schizophrenia, tend to be transient, and are easier to manage through dose adjustments of long-acting antipsychotics. In relatively new cases or previously established recurrent courses of schizophrenia, physicians have higher hopes for better patient compliance and high-quality remission; there are also concerns about side effects, which are harder to manage under the influence of LAI antipsychotics. In periodic forms and during the early stages of the disease, physicians typically combine antipsychotics with mood stabilizers, and they have to prescribe additional oral antipsychotics alongside LAI antipsychotics, or choose combinations of antipsychotics with selective and sedative effects—or even antipsychotic cocktails. The known characteristics of disease progression and the nature of the exacerbations sometimes lead physicians to consider it risky to include such patients in observational studies. Furthermore, they may promptly initiate additional therapy at the first signs of worsening symptoms or even due to dissatisfaction with the effects of LAI antipsychotics. In other words, we are still grappling with our own apprehensions and biases regarding the use of long-acting antipsychotics. These factors can influence clinical judgments about the effectiveness of a particular drug or its specific dosage form.

This study showed that a 12-month course treatment with different dosage forms of paliperidone, administered at flexible doses according to clinical needs, results in a statistically significant improvement in the primary efficacy endpoint — the final PSP score — as well as statistically significant and clinically meaningful improvements in secondary efficacy endpoints, such as the total scores of dimensional scales assessing the severity of psychopathological manifestations of schizophrenia, as proposed in the DSM-5 and ICD-11 classifications, short psychometric methods for assessing overall disease severity (CGI-S), and the severity of negative symptoms (NSA-4). Overall, the results of this study confirm that any dosage form of paliperidone is equally effective in improving clinical manifestations of schizophrenia and social functioning, and is a well-tolerated treatment option for schizophrenia during the remission phase.

The most notable result in the paliperidone treatment was the improvement in social functioning. By the end of treatment with all three dosage forms of paliperidone, a statistically significant increase in final PSP values was achieved, exceeding the established minimal detectable change for this scale. The slower improvement in PSP in the PP3M group, compared to the OP and PP1M groups, can be explained by the more persistent nature of negative symptoms, which significantly affect social functioning, as well as the longer duration of paliperidone use before inclusion in the PP3M group and, therefore, an earlier achievement of the potential effects of this medication on social functioning and the depletion of available recovery resources.

The analysis of the dynamics of the SQS and CRDPSS domains of positive symptoms during the stabilization phase after a schizophrenic episode with three different forms of paliperidone provided conflicting results. In the overall sample of patients receiving any dosage form of paliperidone, a decrease in the SQS "Positive Symptoms" domain was observed by visit 4. However, in the three compared groups, there was primarily either a slight decrease or fluctuations in the dynamics of the "Positive

Symptoms" domains, and only in the PP1M group was there a statistically significant reduction in the "Positive Symptoms" category by visit 4.

A rapid and significant decrease was observed in the CRDPSS "Hallucinations" and "Delusions" domains in the overall sample by visit 2. However, in the individual observation groups, only the PP1M group showed a statistically significant reduction in the "Hallucinations" domain at visits 2, 3, 4, and 5 compared to the baseline, but with no significant differences between the visits.

No significant changes were observed in the "Delusions" domain in any of the observation categories. It should be noted that the concept of "positive symptoms" encompasses, in addition to hallucinations and delusions, associated features such as agitation, motor dysfunction, disorganized mental activity, and certain affective disturbances. Therefore, tracking changes in such a broad parameter as "positive symptoms" during stabilization and the establishment of remission is challenging and the dynamics of the domains of SQS from ICD-10 and CRDPSS from DSM-5 cannot fully align.

The slowing-down, cessation, or absence of positive dynamics in the CRDPSS "Hallucinations" and "Delusions" domains can be explained by the fact that the observational study was conducted in outpatient settings, where patients were in the process of entering remission of varying quality, with relatively minor fluctuations in the intensity of positive symptoms. Significant weakening of these symptoms was typically observed only in the first weeks or months, after which some kind of ceiling to further improvement was reached. The significant improvement in hallucinations in the PP1M group, in our view, is linked to the fact that, firstly, paliperidone has most often recently been prescribed in this group, which by itself brought about results and, secondly, unlike in the OP group, the medication was able to fully manifest its antipsychotic properties due to uninterrupted use. In contrast, patients in the PP3M group joined after prolonged treatment with PP1M, when the best antipsychotic effects of paliperidone had already been observed. The dispersion curves for "delusions" appear to be the least steep, reflecting the overall resistance to the treatment of delusional ideas, and particularly in the cases with residual delusions. In other words, during the treatment of an exacerbation, affective-delusional symptomatology and delusions as part of hallucinatory-paranoid syndrome rapidly improve. As for chronic interpretation delusions or residual delusional ideas during stabilization and remission, despite therapy, they may persist for many months, or even years, which, in our opinion, is reflected in the results of this study.

The positive dynamics of the dimensional assessment of negative symptoms, particularly pronounced in the CRDPSS "negative symptoms" domain in the overall sample and separately in the PP1M group, can be explained by the fact that reliable relapse prevention ensures a gradual reduction in negative symptoms. The differences observed between the two groups receiving long-acting dosage forms of paliperidone may be related to the fact that the PP3M group included patients with generally more persistent mental disorders, typical of continuous forms of schizophrenia. The reduction in negative symptoms is even more clearly observed using the NSA-4 scale, confirming paliperidone's pronounced anti-deficit effect. The fact that the two groups, which received different dosage forms, experienced a similar reduction in the severity of negative symptoms shows that paliperidone not only has anti-deficit properties with minimal AEs on the cortical dopamine system, but also that through its anti-relapse effect, it creates the necessary conditions and, most importantly, provides enough time to engage resources for a natural restoration of the mental function.

Additionally, prolonged remission under well-monitored therapy creates conditions for the gradual alleviation of depression, which is especially noticeable in the OP group, where patients are first experiencing paliperidone therapy, often after treatment with atypical antipsychotics (AAPs) and with initially more pronounced depressive symptoms. The switch to paliperidone facilitates a recession of post-psychotic depression.

The CGI-S scale, which provides a physician's global synthetic impression of disease severity, actually relies mainly on assessing the severity of psychotic symptoms, and, therefore, in this observation, it has a generally flat character, similar to the dynamics of positive symptoms on the SQS scale.

Treatment with long-acting dosage forms of paliperidone — PP1M and PP3M — was characterized by a higher completion rate, exceeding that of oral paliperidone by 2.5 times, and a significant difference in the mean treatment duration and the distribution of patients continuing medication (using statistical terminology, the "survival" of patients on therapy) in the groups receiving long-acting dosage forms of paliperidone (PP1M and PP3M). The main reason for the premature discontinuation by patients in the OP group was their transition to the long-acting dosage

form of paliperidone — PP1M — based on the treating physician's decision on therapeutic appropriateness or at the patient's request.

It is particularly noteworthy that among the three therapy groups, the PP3M demonstrated the best adherence to the prescribed therapy regimen, included the highest number of patients who fully completed the study, and achieved an incidence of exacerbations or lack of efficacy equal to that of the other groups. This was despite the fact that the PP3M group included the highest number of patients with a continuous course of schizophrenia and, in total, more patients with more treatment-resistant forms of the disease, including continuous and episodic with progressive deficit (F20.00 + F20.01) — 46 patients in total (90.2%).

The use of paliperidone demonstrated not only the effectiveness, but also the safety of the therapy: no serious AEs were recorded in the patients, and any AEs that occurred were mild or moderate. No significant differences were found between the compared groups in terms of the overall frequency of AEs, their specific types, including AEs that led to exiting the study. The slightly more frequent occurrence of AEs, especially those newly identified, in the PO group can be explained by the fact that some patients were receiving paliperidone for the first time, meaning that AEs characteristic of the medication occurred early in their treatment. In contrast, patients in the PP1M and PP3M groups had previously been on paliperidone according to the instructions and shown at least satisfactory tolerability. Among the AEs in all three groups, the most common were mild EPS, weight gain, hyperprolactinemia, and its associated clinical manifestations. The good safety profile of all the forms of paliperidone is consistent with findings from other studies.

Limitations

This study was observational and attempted to tack as close as possible to real-world clinical practice. It was not blinded, did not involve randomization, and used straightforward inclusion criteria and the simplest tools to assess symptom severity. The observational design of the study led to selective inclusion in different observations. For example, in the OP group, half of the patients had never previously received paliperidone and more often included were cases with periodic forms of schizophrenia and shorter observation periods. In contrast, the PP3M group more frequently consisted of patients with continuous forms of schizophrenia, who typically experience more pronounced and persistent negative symptoms, consistently exhibit poorer social functioning, and, most importantly, lower sensitivity to any antipsychotic therapy. Such preferential selection may have influenced the lag in the dynamics of many scales for assessing positive and negative symptoms, and most notably, the social functioning indicators, which likely explains the slower dynamics in the parameters of the positive and negative symptom scales and, especially, the delayed recovery in social functioning.

The study design did not include a scale assessment for patients who withdrew from the observation, and during the analysis, imputation of missing data was not performed, because the goal of the study was to analyze the treatment characteristics in real-world clinical practice settings for patients who adhered to therapy throughout the observation period. However, the lack of accounting for data from the withdrawn patients could have led to distorted results due to a "survivorship bias," where cases of unsuccessful therapy with premature discontinuation remain unexamined.

The observational nature of the study as well as its implementation in routine medical practice predetermined the limited sample size in each of the therapy dimension. While the total number of patients receiving different forms of paliperidone allowed for identifying general trends in the dynamics, the minimally acceptable sample size in each of the compared groups could have created conditions for a Type II error in inter-group comparisons.

The choice of brief psychometric scales, such as NSA-4, CRDPSS, and SQS, was also dictated by the observational design, within which the use of more reliable and precise, widely accepted, methods for quantitative assessment, common in RCTs, was challenging and beyond the scope of routine medical practice. The scales used were less accurate, limiting the possibilities of statistical analysis. This may be why statistically significant differences were not found between the samples of patients receiving different forms of paliperidone. However, it is likely that the extended observation period allowed us to obtain convincing, statistically significant differences in the dynamics of the general condition, specific psychopathological symptoms, and the level of social functioning.

CONCLUSION

In this 12-month observational study of the dynamics of psychosocial functioning and psychopathological symptoms in patients with paranoid schizophrenia who

received three different dosage forms of paliperidone during their remission phase in real-world clinical practice settings, statistically significant and clinically meaningful improvements were detected in the overall mental state and specific schizophrenia symptom groups – positive, negative, depressive symptoms, and, especially, social functioning. Therapy with injectable dosage forms was characterized by a longer treatment duration and a higher frequency of completion of the observation period. Therapy with both oral and injectable paliperidone was well tolerated, and among the side effects, extrapyramidal symptoms, hyperprolactinemia and its clinical manifestations, increased appetite, and moderate weight gain predominated. These side effects generally align with those described in RCTs and listed in the instructions for the use of the drug.

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The Use of Melatoninergic Antidepressants for Stabilization of Remission in Depression Comorbid with Alcohol Abuse, Anxiety or Neuropsychiatric Disorders: A Systematic Review

Применение мелатонинергических антидепрессантов для стабилизации ремиссии при депрессии, коморбидной с алкоголизмом, тревожными расстройствами и нейропсихиатрическими заболеваниями: систематический обзор

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Review

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ABSTRACT

BACKGROUND: Depression is one of the most common mental disorders and is associated with a significant increase in the risk of mental and somatic comorbidities. The chronobiological theory of the pathogenesis of depression explains the relationship between the symptoms of depression and disturbance of circadian rhythm regulation. Disrupted circadian rhythms are also observed in other disorders such as alcohol use disorder, anxiety disorders, epilepsy, and Parkinson's disease. Therefore, there is a growing interest in the use of medications with a melatoninergic mechanism of action in the treatment of depression comorbid with the aforementioned disorders.

AIM: This review aims to systematically examine the evidence for the use of melatoninergic antidepressants (agomelatine and fluvoxamine) in the treatment of depression comorbid with alcohol abuse, anxiety disorders (including phobic anxiety, panic, and generalized anxiety disorders), or neuropsychiatric disorders (such as epilepsy and Parkinson's disease).

METHODS: This systematic review included experimental studies, systematic reviews, and meta-analyses published in English and Russian, which examined the use of fluvoxamine and agomelatine in adult patients with recurrent depressive disorder (ICD-10) or major depressive disorder (DSM-5) comorbid with alcohol abuse, anxiety or neuropsychiatric disorders. The search was conducted in the PubMed, Cochrane Library and eLIBRARY scientific databases. The quality of the selected studies was assessed using the Cochrane Risk of Bias tool, which is used to evaluate the risk of systematic errors in clinical studies. The results were presented as a narrative synthesis and grouped by the comorbidities evaluated.

RESULTS: A total of 20 articles were reviewed (with a pooled sample size of n=1,833 participants). The results suggest that melatoninergic antidepressants might help in reducing depressive and anxiety symptoms, improve sleep, decrease alcohol cravings, and alleviate the severity of motor symptoms in Parkinson's disease. Moreover, the use of pharmacogenetic testing to select the medication and dosage may enhance its therapeutic effectiveness.

CONCLUSION: The review demonstrates a significant lack of clinical data and guidelines on the use of melatoninergic medications for the treatment of depression comorbid with other disorders. In this regard, it is currently difficult to draw a definitive conclusion regarding the efficacy and safety of agomelatine and fluvoxamine in the treatment of these comorbidities. Available studies suggest an improvement in the clinical manifestations of the comorbidities. Future research directions might include the development and implementation of double-blind, randomized clinical trials to study the use of melatoninergic medications in patients with depression comorbid with other disorders.

АННОТАЦИЯ

ВВЕДЕНИЕ: Депрессия является одним из самых распространенных психических заболеваний, при котором существенно увеличивается риск развития сопутствующих психиатрических и соматических расстройств. Хронобиологическая теория патогенеза депрессии объясняет взаимосвязь депрессивных симптомов с нарушениями регуляции циркадного ритма. Изменения циркадного ритма также наблюдаются при других заболеваниях: синдроме зависимости от алкоголя, тревожных расстройствах, эпилепсии и болезни Паркинсона. В связи с этим, растет интерес использования препаратов с мелатонинергическим механизмом действия в терапии депрессии, коморбидной с вышеперечисленными расстройствами.

ЦЕЛЬ: Целью данной работы является систематический обзор исследований, рассматривающих применение мелатонинэргических антидепрессантов (агомелатина и флувоксамина) для лечения депрессии, коморбидной с алкогольной зависимостью, тревожными расстройствами (тревожно-фобическое, паническое, генерализованное тревожное расстройство), или нейропсихиатрическими заболеваниями (эпилепсия, болезнь Паркинсона).

МЕТОДЫ: Для проведения систематического обзора отбирались экспериментальные исследования, систематические обзоры или мета-анализы, опубликованные на английском и русском языках, и описывающие применение флувоксамина и агомелатина в группах взрослых испытуемых, имеющих коморбидный диагноз рекуррентного депрессивного расстройства (согласно МКБ-10) или большого депрессивного расстройства (согласно DSM-5) с алкогольной зависимостью, тревожными расстройствами или нейропсихиатрическими заболеваниями. Поиск осуществлялся в научных базах PubMed, Cochrane Library и eLIBRARY. Качество отобранных исследований оценивалось с помощью Кокрейновского инструмента по оценке рисков систеатмическиих ошибок (Cochrane Risk of Bias tools). Результаты были представлены в виде нарративного синтеза и сгруппированы в соответствии с изучаемыми коморбидными состояниями.

РЕЗУЛЬТАТЫ: Всего было рассмотрено 20 статей (общая численность участников *n*=1833 человек). Результаты предполагают, что мелатонинергические антидепрессанты могут способствовать уменьшению депрессивной и тревожной симптоматики, улучшению сна, а также снижению влечения к употреблению алкоголя и выраженности двигательных симптомов болезни Паркинсона. Кроме того, использование фармакогенетического тестирования для выбора препарата и дозировки может повышать его терапевтическую эффективность.

ЗАКЛЮЧЕНИЕ: Результаты обзора выявляют выраженный недостаток клинических данных и руководств по применению препаратов с мелатонинергическим механизмом действия при депрессии, сочетанной с другими состояниями. В связи с этим на данный момент затруднительно сделать однозначный вывод об эффективности и безопасности применения агомелатина и флувоксамина при данных коморбидных нозологиях. Существующие исследования свидетельствуют об улучшении проявлений сочетанной симптоматики рассмотренных заболеваний. Дальнейшие направления исследований могут включать разработку и проведение двойных слепых рандомизированных клинических исследований по изучению применения мелатонинергических препаратов при депрессии, коморбидной с другими заболеваниями.

Keywords: *melatoninergic antidepressants; depression; anxiety disorders; alcohol abuse; epilepsy; Parkinson's disease*
Ключевые слова: *мелатонинергические антидепрессанты; депрессия; тревожные расстройства; алкоголизм; эпилепсия; болезнь Паркинсона*

INTRODUCTION

Depression is one of the most prevalent mental disorders. In a global survey conducted by the WHO (World Health Organization), between 13.7% and 22% of respondents across various countries reported experiencing symptoms of depression in the preceding 12 months [1]. The prevalence of depression has been steadily increasing in recent years, partly due to the pandemic [2]. The presence of depressive symptoms significantly raises the risk of developing other mental and somatic disorders, including anxiety, substance dependence, neurodegenerative diseases, and other neurological conditions [3, 4]. According to some estimates, the comorbidity of depression with other mental health disorders ranges from 36.7% to 73.5% [5]. The presence of a comorbid condition with depression complicates treatment. It increases healthcare utilization while reducing adherence to treatment, makes it more difficult to select appropriate pharmacological therapies, and overall worsens disease outcomes [6]. At the same time, successful treatment of depressive symptoms is associated with a significant reduction in the clinical symptoms of the comorbid condition [7]. It is also worth noting that selection of pharmacological treatments for comorbid disorders is challenging, because randomized clinical trials for drug development often exclude participants with concurrent mental, neurological, or physical disorders [8]. Thus, studying and developing new approaches to treating depressive disorders comorbid with other mental and physical disorders is of significant research and practical importance.

The pathophysiological mechanisms underlying depression remain poorly understood. The chronobiological theory explains the connection between depressive symptoms and disruptions in sleep and circadian rhythms regulation as one of the most commonly observed symptoms [9–11]. Desynchronization of physiological rhythms may include reduced slow-wave sleep, shortened rapid eye movement

(REM) sleep latency, disruptions in REM/non-REM cycles [12], daytime sleepiness [13], altered daily temperature patterns [14], and may vary from within-day to seasonal fluctuations [14, 15]. Sleep and circadian rhythm disruptions often occur in depression and typically persist across different stages of the disorder, including the prodromal period, acute episodes, and remission phases [16]. These disruptions may increase the risk of developing depression, exacerbate the symptoms of existing depressive disorders, reduce the quality of remission, and increase treatment resistance [17, 18]. However, a definitive explanation of the connection between chronobiological disturbances and depressive symptoms has yet to be established. One theory suggests that the simultaneous dysregulation of the circadian system and serotoninergic functions may be a contributing factor [19].

Melatonin, a serotonin metabolite and the primary hormone of the pineal gland, plays a key role in regulating circadian rhythms [20–22]. Additionally, disruptions in melatonin regulation are associated with impaired cardiovascular and immune system function, carcinogenesis, increased oxidative stress, and a number of other processes [19]. Given that depression is characterized by reduced melatonin levels, some researchers describe depression as a "low-melatonin syndrome" [19, 20].

Modern approaches to the treatment of depression are primarily grounded in monoamine theories of its pathophysiology and involve the use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, which are known to increase extracellular concentrations of monoamine neurotransmitters [21]. However, these antidepressants do not alleviate, and in some cases may worsen, sleep disturbances and disruptions of circadian and/or seasonal rhythms associated with depressive disorders [12, 22, 23].

Given the presence of chronobiological disturbances in depression and evidence regarding their treatment with the goal to reduce depressive symptoms, there is growing interest in the use of melatoninergic compounds. Agomelatine is the first authorized antidepressant whose action is primarily directed at the melatoninergic system. It acts as an agonist of the MT1 and MT2 melatonin receptors and as an antagonist of the 5HT2C serotonin receptor. Clinical studies indicate that agomelatine is comparable to other antidepressants in its ability to reduce symptoms of depression and anhedonia but surpasses them in how it improves sleep parameters with minimal side effects [15, 23–26]. However, some reports suggest that agomelatine may negatively affect liver function, and its long-term toxicity currently remains unclear [23, 24]. Fluvoxamine is an antidepressant belonging to selective serotonin reuptake inhibitors that also inhibits the catabolism of melatonin by suppressing the activity of the CYP1A2 and CYP2C19 cytochromes — enzymes involved in the metabolism of endogenous melatonin. This action increases nocturnal melatonin concentrations in the blood [27, 28]. While fluvoxamine is widely used to alleviate depressive symptoms, studies on its effects on circadian rhythms are limited and inconsistent. One study reported a worsening of sleep characteristics with fluvoxamine [29], whereas another noted significant improvements in sleep disturbances and polysomnographic parameters [30].

Comorbid depression and alcohol abuse

The prevalence of alcohol abuse and alcohol abuse among patients with depressive disorders significantly exceeds that in the general population, reaching 21–30% among patients with depression compared to 16% in the general population [31, 32]. Notably, some studies report even higher rates of these comorbid conditions (e.g., Kurhaluk [33] reports prevalence ranging from 12% to 79%), which may be explained by the heterogeneity of the included nosological entities for depression and alcohol abuse.

Comorbidity of depression and alcohol abuse is 2–3 times more common in men [31, 34] and is associated with the presence of anxiety and personality disorders [34]. The high prevalence of this combination of disorders may be attributed to both hereditary factors and the shared neurobiological mechanisms involved in both conditions [31, 35, 36]. Comorbid depression and alcohol abuse are associated with greater severity and duration of both conditions, an increased risk of suicide, increased resistance to treatment, a higher number of hospitalizations, reduced quality of life, a higher recurrence rate, and elevated mortality [32, 34, 35, 37–39]. The presence of depressive symptoms alongside alcohol abuse also complicates disease diagnosis [31, 40, 41], particularly in determining whether the depressive state is secondary to alcohol abuse or precedes it. Comorbidity also poses challenges in selecting effective pharmacological treatments that can significantly reduce the symptoms of both conditions [40, 42, 43].

One approach to developing effective treatments for comorbid conditions is the assessment of the shared

mechanisms underlying both disorders. As with the previously mentioned chronobiological approach to understanding the pathogenesis of depressive disorders, alcohol abuse is also characterized by circadian rhythm desynchronization, which, according to some studies, may serve as a marker of addiction severity [44]. Research indicates that even a single intake of a small dose of alcohol can alter body temperature, while a high dose affects the cortisol and melatonin levels; more significant and prolonged disruptions in melatonin production occur with the development of alcohol abuse [33, 38, 44]. Cravings for alcohol, as a form of reward-seeking motivation, may also be associated with circadian rhythms, alongside other personality and environmental factors [45, 46]. Further evidence of the link between circadian rhythms and alcohol abuse comes from findings indicating that individuals prone to late sleeping and waking patterns — the so-called "night owls" — are more predisposed to developing substance dependence [33, 44–46].

In this context, the study of pharmacological agents affecting the melatoninergic system (e.g., agomelatine and fluvoxamine) in comorbid depression and alcohol abuse holds significant theoretical and practical value.

Comorbid depression and anxiety disorders

Researchers believe that comorbid mental disorders in patients with depression are more the rule than the exception. It is widely acknowledged that depression and anxiety disorders (AD) often occur simultaneously, and that the presence of one disorder increases the risk of subsequent development of the other (comorbid) condition. Estimates suggest that the prevalence of AD in depressive patients ranges from 40% to 60% [47, 48]. Furthermore, comorbidity of depression and AD is associated with greater symptom severity and an increased risk of suicide [49]. There is also a high prevalence of alcohol and other psychoactive substance (PAS) abuse in this group of patients [50–52]. It is worth noting that depression combined with AD is associated with difficulties in social functioning and contributes to the disease burden and strain on the health care system. Some studies report lower levels of education, higher unemployment rates, and a history of childhood trauma in these patients [50, 53]. Despite numerous studies indicating common pathophysiological mechanisms in the development of both depression and AD, as well as the effectiveness of similar pharmacological treatments (e.g., SSRIs), treatment-resistant cases are more common among comorbid patients compared to those with a single disorder [54, 55]. Similar findings are reflected in the study by van Balkom et al. [56], where the presence of comorbid AD in patients with depression was associated with inadequate response to therapy, a reduced likelihood of positive outcomes, and a lower remission rate [56]. Therefore, improving treatment approaches for this group of patients is of significant practical importance. Research on the etiopathogenetic mechanisms of depression and AD continues. A particular focus is put on the chronobiological concept [57–59]. Given the disruption of melatonin metabolism, circadian rhythm desynchronization, and associated sleep disturbances seen in both depression and AD patients, evaluating drugs with melatoninergic effects (agomelatine, fluvoxamine) appears promising [60–62]. Despite the growing number of studies on the effectiveness of this drug class in depression and AD, there remains a lack of systematic data on their effectiveness and safety in cases of comorbidity.

Comorbid depression and epilepsy

Depressive disorder is one of the common manifestations of psychopathological disturbances observed in epilepsy as a consequence of chronic brain epileptization, significantly complicating the course of the underlying disease. In patients with uncontrolled seizures, the prevalence of depressive disorder ranges from 20% to 55% [63].

In a large study, sleep disturbances were observed twice as frequently in patients with epilepsy compared to the control group. The most common sleep disturbances in epilepsy patients include excessive daytime sleepiness, insomnia, and sleep-related breathing disorders [64, 65]. Melatonin plays a special role in maintaining sleep. It has neuromodulatory properties, exerts an inhibitory function in the central nervous system, and regulates circadian rhythms. Melatonin has antioxidant, neuroprotective, anticonvulsant, and anxiolytic effects. Various experimental models have shown that melatonin treatment, administered before or after kainic acid (KA)-induced status epilepticus, affects oxidative stress and the development of epileptogenesis. Melatonin treatment suppresses KA-induced seizure activity [66].

Despite the development of numerous antiepileptic drugs (AEDs) since the introduction of phenobarbital in 1912, the issue of seizure control remains relevant to this day. Polytherapy often leads to a number of adverse events, including neurological disturbances (drowsiness,

ataxia, dizziness), mental and behavioral symptoms, as well as metabolic changes [67–69]. The need for better tolerability of AEDs for this group of people is even more pressing. The use of drugs with melatoninergic effects may be promising in maintaining seizure control, optimizing the tolerability of antiepileptic therapy, stabilizing comorbid mental disorders, and improving sleep quality [70, 71].

Comorbid depression and Parkinson's disease

The types of depressive disorders observed in Parkinson's disease (PD) include major depression, minor depression, and dysthymia. Patients with mild depression may not formally meet the criteria for a depressive disorder according to DSM-5, but the distressing symptoms significantly complicate the primary disease [72, 73]. Most cases of affective fluctuations in PD may represent episodes of mild or recurrent subsyndromal depression [74, 75]. It has been noted that the profile of depressive symptoms is not identical to the profile of idiopathic depression. Patients with PD tend to show higher levels of anxiety, intact short-term memory, and lower levels of suicidality [76].

The assessment of depression prevalence in PD is complicated by the overlap of somatic symptoms with coexisting cognitive issues and the side effects of dopaminergic drugs [77], and also depends on the approach used to evaluate depression in PD: the "inclusive" approach, where the presence of a symptom is assessed regardless of its origin, leads to a higher prevalence rate compared to the "exclusive", diagnostic-etiological approach [78].

According to various researchers, depressive symptoms are present in approximately 20–30% of PD patients, with figures ranging from 2.7% to 90% in the available literature for this population [72, 79–83]. Between 20% and 25% of patients receiving specialized care are on antidepressants [84–86]. In the review by Reijnders et al. [79], the average prevalence of major depressive disorder was 17–24.8%, the prevalence of mild depressive symptoms was 22%–36.6%, and dysthymia was found in 13–22.5% [79, 87].

The risk factors for depression in patients with PD include female sex, late stages of PD, and the presence of cognitive impairments in the clinical presentation [72, 88].

The mechanism behind the onset of depression is not yet fully understood. The condition may result from the development of an endogenous disorder, a reaction to disability, an inherent part of PD, or a combination of any of these causes [81]. Pathogenetically, depression in PD is linked to the progression of neurodegenerative processes in the ventral striatum and mesolimbic dopaminergic denervation [89]. At the same time, depression may be associated with motor fluctuations and dyskinesias, which are more commonly seen in carriers of the *G2019S* mutation [90, 91]. Prognostically, it is known that depression has a significant impact on the prognosis of the primary disease: patients score lower on motor function and activities of daily living (ADL) scales, report more cognitive impairments, and a lower quality of life [92–94]. Additionally, there is an increased risk of uncontrolled use of antiparkinsonian drugs [95] and the burden on caregivers increases [96].

Sleep disturbances are registered in 40–90% of PD patients [97]. The major risk factors for insomnia include female sex, duration of the primary disease, the presence of anxiety-depressive disorders, characteristics of dopaminergic therapy, and circadian dysfunction [98, 99]. It should be noted that additional evidence is accumulating on circadian rhythm disturbances in PD as an important factor in the high incidence of insomnia in PD patients [100]. Several studies have shown a link between changes in the melatonin secretion profiles and the severity of PD symptoms [101, 102], as well as sleep disturbances in PD [103]. Additionally, the studies demonstrated a reduction in melatonin secretion amplitude in PD patients compared to the age-matched control group [104, 105]. Currently, the data is insufficient on the effectiveness and safety of any class of antidepressants for the treatment of PD to provide recommendations for their use [81, 106].

Thus, this study aims to provide a systematic review of studies on the use of antidepressants with a melatoninergic action (fluvoxamine and agomelatine) for the treatment of depression comorbid with alcohol abuse, anxiety disorders (phobic anxiety, panic, and generalized anxiety disorder), and neuropsychiatric diseases (Parkinson's disease, epilepsy).

METHODS

The work on the systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [107] and was carried out in several stages:

1. Development of the study protocol, including the main objectives of the work, inclusion and exclusion criteria, and the search algorithm;
2. Pre-registration of the review in the PROSPERO system (registration number #CRD42024536658);
3. Search and selection of relevant research studies;

4. Analysis of selected studies and quality assessment;
5. Narrative synthesis of the obtained results, including the description and evaluation of the effectiveness of the intervention under consideration.

The PICO system [107] was used in developing the search strategy for the systematic review.

Eligibility criteria

The inclusion criteria were the followings:

- Participants: Adults with recurrent depressive disorder comorbid with anxiety disorders (phobic anxiety, panic, and generalized anxiety disorder), alcohol abuse, Parkinson's disease, epilepsy.
- Intervention: The use of antidepressants with melatoninergic action (fluvoxamine or agomelatine).
- Comparison: Studies with or without a control group.
- Outcomes: Primary — change in depressive symptoms; secondary — change in symptoms of the comorbid condition (alcohol abuse, anxiety disorders, epilepsy, Parkinson's disease).
- Study design: Any experimental design, systematic reviews, meta-analyses.

Exclusion criteria:

- Publication language: Articles written in languages other than Russian or English.
- Publication type: Studies that had not undergone a formal peer review process (e.g., conference abstracts) were excluded from the review.

Information sources

The search for the scientific articles was conducted in the following databases: PubMed, the Cochrane Library, and eLIBRARY. The choice of specific databases, as well as their number, was based on existing recommendations [108–110], as well as their availability to the authors of this study. Subsequently, both forward and backward searches were performed; i.e., searching the bibliographies of selected articles and among articles citing the identified materials. When possible and necessary, full-text versions of the articles were requested from the corresponding authors, as well as potential recommendations for other works related to the review.

Search strategy

In the PubMed and the Cochrane Library systems, the search was performed using controlled and contextual keywords with Boolean operators. The search was conducted by a group of six co-authors independently from each other, following a predefined search algorithm. The search algorithm for each of the scientific databases is presented in Appendix 1 in the Supplementary.

Analysis of the results

The results of the search and selection of articles were graphically presented in the form of a flowchart in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2020) guidelines [111, 112] for each of the comorbid conditions (see Figures 1–4). The data from the identified publications were entered into an electronic spreadsheet consisting of the following sections: bibliographic details of the article, study design, participant characteristics, study setting, characteristics of the control group, recruitment procedure, diagnosis in the group, research methods used, clinical indicators before intervention, details of the pharmacological treatment, additional pharmacological or psychosocial interventions received by participants, study goal, study duration, detailed description of primary outcomes, detailed description of secondary outcomes, negative side effects of the drug, other study outcomes, and quality assessment of the study. Missing data were requested from the study authors when necessary and possible. The search and selection of articles were undertaken multiple times from April 21, 2024, to June 15, 2024. Disagreements regarding the selected articles were resolved through discussion and consultation with other co-authors. All participants had sufficient knowledge of English to perform the search, selection, and analysis of scientific materials.

The quality of the selected studies was assessed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [107] using the Cochrane Risk of Bias tools [113]. Researchers independently considered potential sources of bias in the study results. Any disagreements regarding the assessment of potential biases were resolved through discussion or consultation with other co-authors.

The results of the studies that met the inclusion criteria and were available in full-text format were analyzed and included in the review. Results were synthesized in a narrative format and grouped according to the studied comorbid conditions. The primary indicators reflected in the results included the impact of fluvoxamine or agomelatine on depression symptoms, symptoms of comorbid conditions (alcohol abuse, anxiety disorders,

epilepsy, Parkinson's disease), as well as the potential side effects of these medications. The results of the review were presented in tabulated format.

RESULTS

Comorbid depression and alcohol abuse

Based on the search algorithm, 277 publications were found, including 35 duplicates. Subsequently, 228 publications were excluded due to failure to meet eligibility criteria and 3 due to the unavailability of full-text versions. As a result, 11 publications were selected for further review. The study selection algorithm for the systematic review is shown in the flowchart (Figure 1).

Upon further assessment of eligibility, two studies were excluded due to insufficient data for the analysis provided in the article, eight studies were excluded since the condition in the study participants did not meet the eligibility criteria, and one study was excluded since the study type did not meet the eligibility criteria.

In most of the experimental studies, the sample of participants consisted of patients with mixed affective symptoms comorbid with alcohol abuse — mood disorders

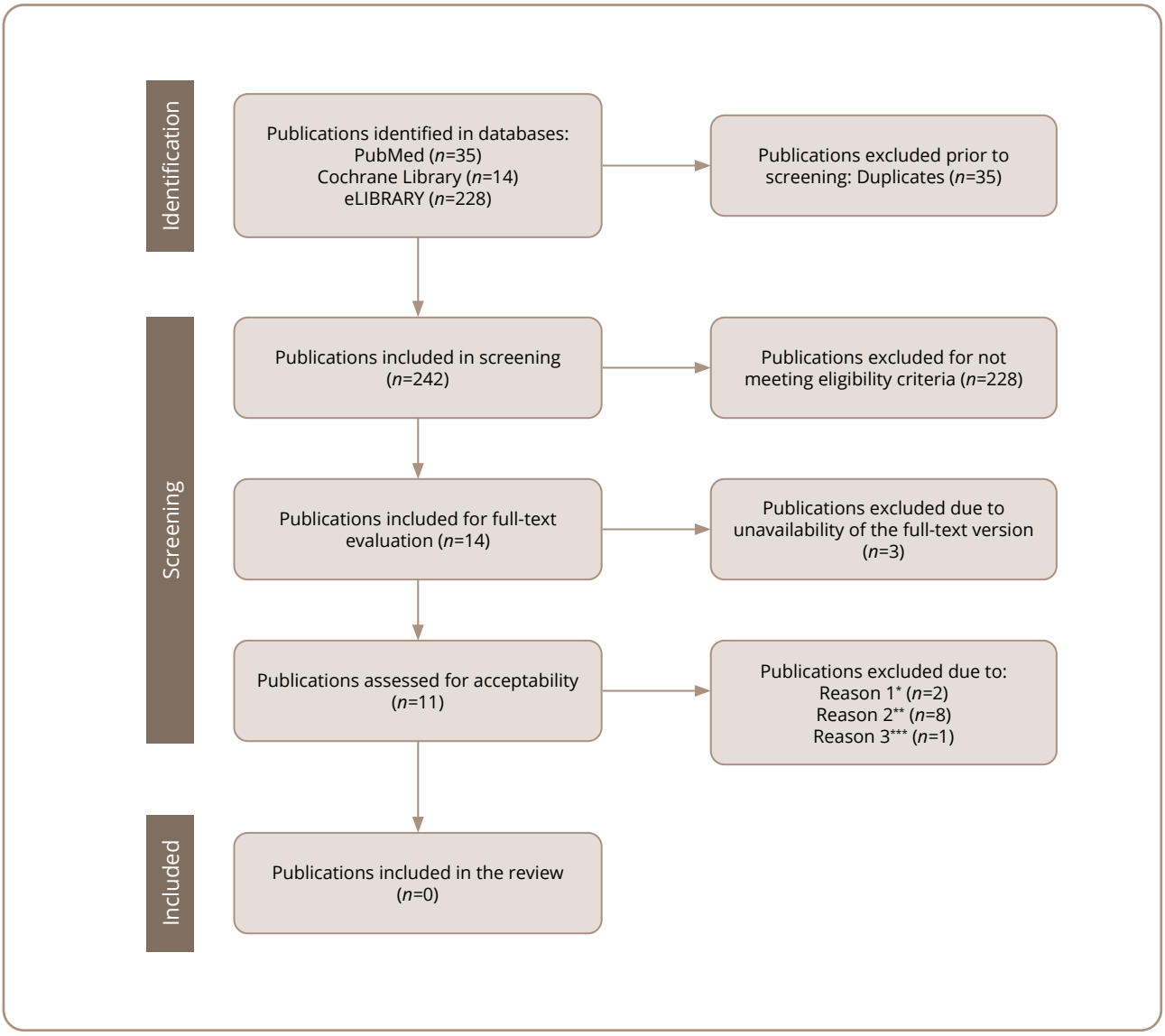


Figure 1. PRISMA flow chart demonstrating the selection process of comorbid depression and alcohol abuse studies.

Note: * — insufficient data provided in the article for analysis; ** — diagnosis of the study participants did not meet the eligibility criteria; *** — study type did not meet the eligibility criteria.

Source: Klimanova et al., 2024

or obsessive-compulsive disorder [114], depressive episode (F32), or cyclothymia (F34) [115, 116]. Three studies included patients with comorbid alcohol abuse and a depressive episode (F32) [117–119]. In two studies, the diagnosis of the participants was not indicated [120, 121]. However, due to the limited data on the use of melatoninergic antidepressants in depression comorbid with alcohol abuse, these studies will be considered in more detail. The main characteristics of the studies reviewed are presented in Table S1 in the Supplementary.

All of the listed studies investigated the effect of fluvoxamine on comorbid depressive symptoms and alcohol abuse. It is also worth noting that seven of the reviewed studies were published by the same group of researchers based on the results of one sample of participants [115–121]. In general, all studies had relatively small sample sizes, ranging from 45 to 175 participants (a total of *n*=819 participants), with the majority of participants being male. Psychometric scales were used to assess affective symptoms, including the Hospital Anxiety and Depression Scale (used in all studies), the Hamilton Depression Rating Scale [115–121], the Beck Depression Inventory [119, 120], and the Montgomery-Åsberg Depression Rating Scale [114]. For assessing alcohol cravings, the Visual Analogue Scale (used in all studies), the Penn Alcohol Craving Scale [115, 116, 118–121], and the Scale of Pathological Addiction [116, 120, 121] were used. None of the studies formally assessed sleep disturbances. The Naranjo algorithm [114] and the UKU Side Effect Rating Scale [115–121] were used to assess adverse events. Assessments were performed on days 1, 7, 14, and 30 [114] and days 1, 9, and 16 of medication use [115, 116, 118–121]. The fluvoxamine dose in the studies ranged from 50 to 200 mg per day in one study [114] and 100 mg/day [50; 150] (Md [Q1; Q3]) in other studies [115, 116, 119—121]; none of the studies presented a methodology for determining or increasing the medication dosage. Three studies included comparison groups and a randomization procedure. In one case, the outcomes for participants receiving fluvoxamine were compared with those receiving other antidepressants [114]; in two other studies [115, 116], the effectiveness of medication prescriptions (fluvoxamine, mirtazapine, and carbamazepine) was compared based on the principle of generating recommendations for choosing a medication and its dose based on pharmacogenetic testing, and without it.

One of the reviewed studies [114] indicated that fluvoxamine use contributes to a reduction in anxiety, depressive symptoms, and alcohol cravings, with the therapeutic effect being achieved by day 7 — faster compared to other antidepressants. The other studies also demonstrated a trend toward a decrease in anxiety, depression symptoms, and clinical manifestations of alcohol abuse following fluvoxamine administration [115, 116, 118–121]. All studies confirmed that fluvoxamine use did not result in significant negative or adverse effects. Additionally, some studies indicated the influence of the CYPD6 polymorphism on fluvoxamine efficacy and safety: participants with the GA genotype experienced a significantly greater reduction in depressive symptoms and a significantly slower onset of adverse effects compared to those with the GG genotype [119, 120].

No studies of agomelatine in a group with comorbid conditions were identified during the systematic search. However, isolated pilot studies on sleep disorders in alcohol abuse suggest that agomelatine may help reduce sleep disturbances in patients with alcohol abuse [122]. In another observational study, it was noted that agomelatine use in patients with major depressive disorder and alcohol abuse could lead to irreversible deterioration in liver enzyme parameters [123].

Thus, the available research suggests that fluvoxamine and agomelatine may be effective in reducing depressive symptoms, sleep disturbances, and alcohol cravings. However, due to the limited number of studies, it is currently impossible to draw definitive conclusions about the efficacy of these medications in alleviating affective disorders and improving circadian rhythms in patients with alcohol abuse.

Comorbid depression and anxiety disorders

Based on the search algorithm, 444 publications were identified, of which 288 were excluded, and 156 were thoroughly reviewed. During the screening process, an additional 77 publications were excluded due to the unavailability of full-text versions. Consequently, 79 publications were selected for eligibility assessment. The study selection algorithm for the systematic review is shown in the flowchart (Figure 2).

Despite the high prevalence of comorbid anxiety disorders among individuals with depression, current research on antidepressant therapy for comorbidities is extremely limited [124]. Instead, most studies focus on anxiety symptoms as part of depressive disorders and evaluate the effectiveness of treatment based on these symptoms. Given the lack of articles fully meeting the eligibility criteria

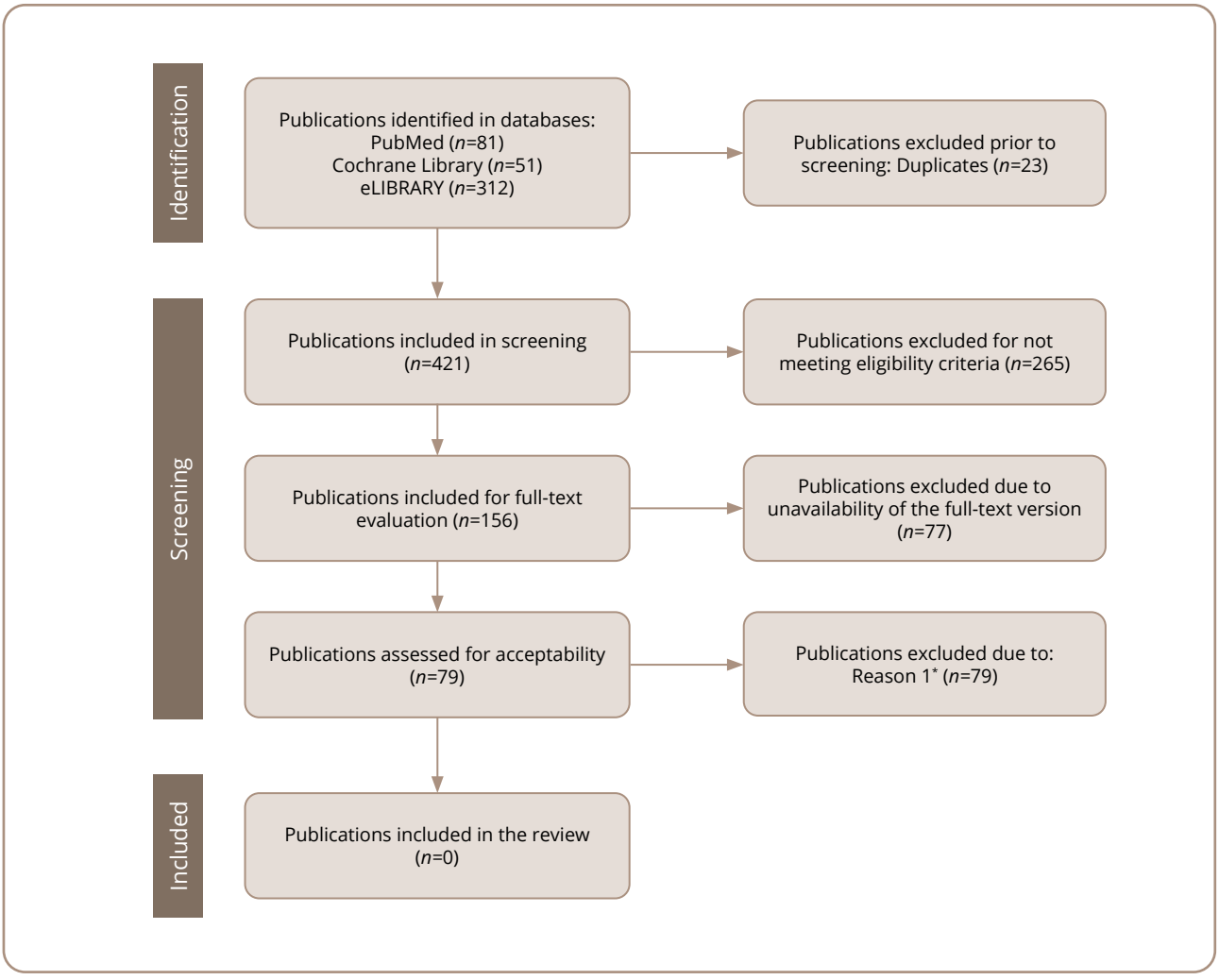


Figure 2. Flow chart demonstrating the selection process of comorbid depression and anxiety disorders studies.

Note: * — did not meet eligibility criteria (diagnosis, publication type).

Source: Klimanova et al., 2024

for this systematic review, seven original studies conducted in Russia were reviewed in detail [125–131]. These studies assessed the effectiveness of the antidepressants under consideration in cases of anxiety-depressive disorder (F41.2) [125], adjustment disorder with mixed anxiety and depressed mood (F43.2) [130], anxiety-depressive spectrum conditions associated with chronic somatic disorders [127], and in a group of patients with various forms of depressive disorders with elevated anxiety indicators according to psychometric evaluations [126, 128–130]. The main characteristics of the reviewed studies are presented in Table S2 in the Supplementary.

The total number of participants was *n*=784; however, it should be noted that two studies [128, 130] were conducted on the same study sample. Six articles investigated the use of agomelatine [125–130]; and one studied, fluvoxamine [131]. In all studies [125–131], participants were recruited from inpatient and outpatient mental-health clinics; however, the participant recruitment procedures were not specified. In each study [125–131], the majority of participants were women (64% to 84%). Standardized psychometric scales were used to evaluate the efficacy of the medications, assessing depression and anxiety [125–131], anhedonia [127], sleep quality [126–129], quality of life [124], and overall clinical impression [126, 128–131]. To monitor adverse events and assess tolerability, scales for evaluating side effects were used [126, 128, 130, 131], along with general health assessments, including blood pressure measurements, heart rate, and blood chemistry analysis, among others [128, 130, 131]. Agomelatine was prescribed

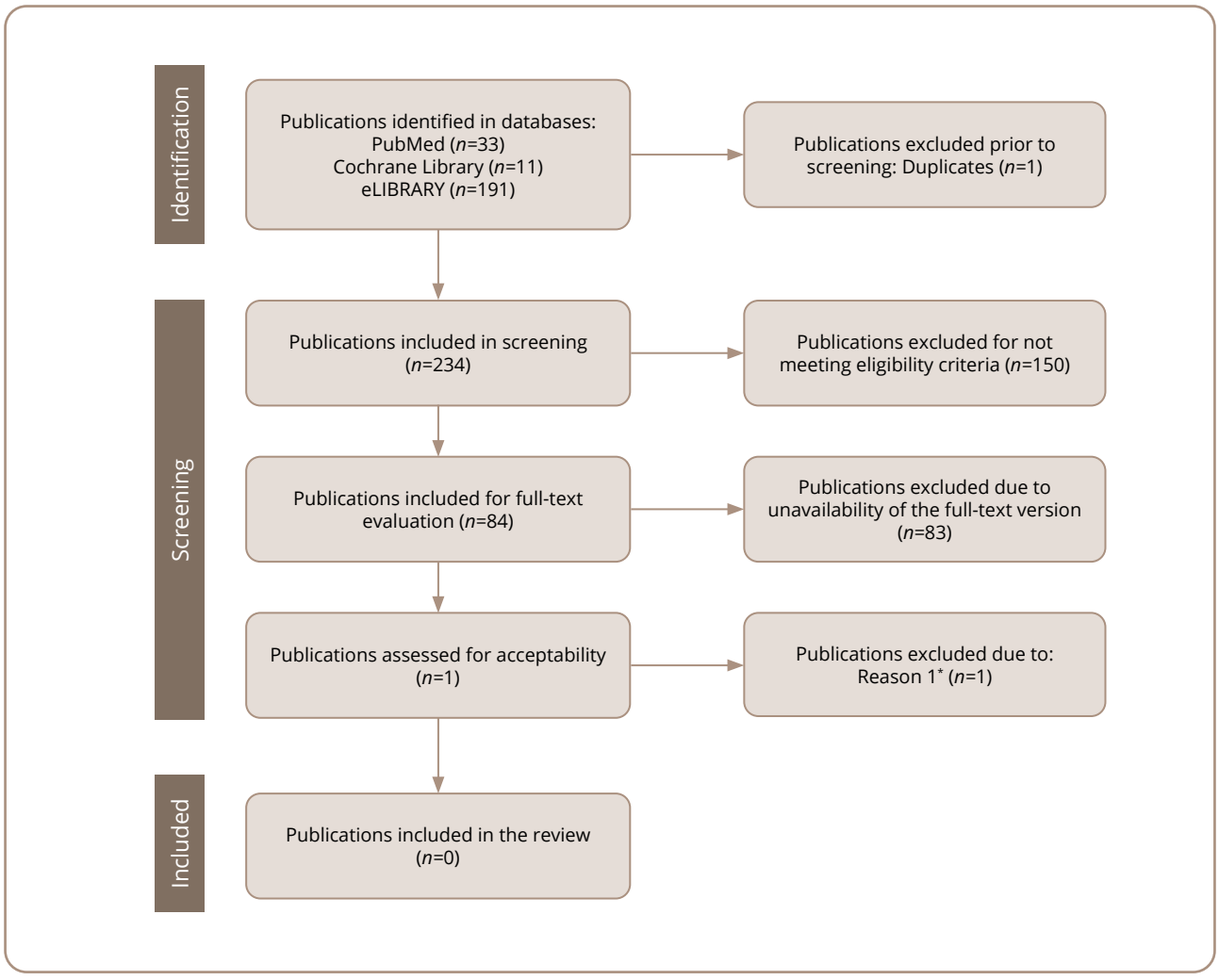


Figure 3. Flow chart demonstrating the selection process of comorbid depression and epilepsy studies.

Note: *— did not meet eligibility criteria (diagnosis).

Source: Klimanova et al., 2024

at doses of 25–50 mg once overnight, while fluvoxamine was administered at 100–300 mg/day. It was noted that dose increases were decided by the attending physician if the therapeutic effect was insufficient, but the specific methodologies were not detailed. In three studies [128–130], it was noted that other psychotropic medications were used alongside the antidepressants being studied, while other papers did not specify whether additional pharmacological or psychotherapeutic interventions were used. Participants in the agomelatine studies were followed for 6 weeks [126], 8 weeks [128–131], or 3 months [125, 127], while participants in the fluvoxamine study were observed for 8 weeks [131]. Results indicate that the use of these antidepressants led to statistically significant reductions in symptoms of depression and anxiety [125, 126, 127–131], anhedonia [127], and sleep disturbances [125, 127, 129], improvements in the quality of life [125], the severity of mental disorders [126, 129–131], and a decrease in suicidal ideation [128, 130]. These improvements were observed within the first two weeks [125–127, 129, 130]. Remission in depressive symptoms was achieved in approximately 70% of participants [128, 129, 131]. None of the studies reported adverse events that led to participant withdrawal.

However, despite the acceptable design of the studies and data indicating the effectiveness of therapy in reducing anxiety symptoms in depression, these studies could not be included in the current systematic review due to failure to meet the eligibility criteria. One study conducted outside of Russia [132] was dedicated to a theoretical

review of various treatment options and strategies for patients with depression and comorbid, generalized anxiety disorder and was a narrative review, which also served as an exclusion criterion. The conclusions presented by the authors indicate the lack of clinical data and specific guidelines for the treatment of individuals with comorbid depression and anxiety disorders.

Comorbid depression and epilepsy

Based on the search algorithm, 235 publications were found, 1 of which was excluded, and 234 were thoroughly reviewed. During the screening process, an additional 83 publications were excluded due to the unavailability of full-text versions. Consequently, 151 publications were selected for eligibility assessment. The study selection algorithm for the systematic review is shown in the flowchart (Figure 3).

The authors selected one paper for detailed study [133]. The main characteristics of this study are presented in Table S3 in the Supplementary.

However, on closer examination, this study did not meet the eligibility criteria as the study sample in which the antidepressant with melatoninergic action (agomelatine) was studied consisted of patients with epilepsy comorbid with mixed anxiety, depressive symptoms, and sleep disorders. Therefore, it was not clarified whether the aforementioned symptoms reached clinically significant levels or if any of these patients were diagnosed with recurrent depressive disorder according to ICD-10 or major depressive disorder according to DSM-5. However, due to the limited research available at this time on the use of melatoninergic antidepressants in epilepsy comorbid with depression, the study by Jiang et al. [133] will be discussed in more detail.

The aim of this observational cohort retrospective study was to evaluate the effectiveness of agomelatine compared to escitalopram. Participants (n=113) were randomized into one of two groups depending on the medication they received. Group 1 (agomelatine): 52 patients (26 males [50%], mean age 31.5 years, mean age of epilepsy onset 21.5 years, with the majority having epilepsy of unknown etiology 38 [73.08%]; focal seizures 10 [19.23%], bilateral tonic-clonic seizures with focal onset 42 [80.77%]. Most patients received two or more antiseizure medications (n=35; 67.03%)]. Group 2 (escitalopram): 61 patients (34 males [55.74%], mean age 26 years, mean age of epilepsy onset 19 years, with the majority having epilepsy of unknown etiology — 41 [67.21%]; focal seizures — 16 [26.23%], bilateral tonic-clonic seizures with focal onset — 45 [73.77%]. Most participants received two or more antiseizure medication [n=48, 78.69%]). The groups did not differ significantly in terms of demographic or clinical characteristics. The duration of medication use was 8 weeks, with assessments of participants' condition before and after the treatment course. The primary assessment methods used were the Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale, and the Pittsburgh Sleep Quality Index.

The results of the study showed that during the follow-up assessment period after the medication course, Group 1 (agomelatine) had significantly lower levels of anxiety and sleep disturbances (p=0.001) compared to Group 2 (escitalopram), while depression scores in both groups did not differ significantly (p=0.712). Both antidepressants contributed to a reduction in depressive symptoms by an average of 77% from the baseline. A negative correlation was also found between the number of antiepileptic drugs taken and the level of depression (p=0.004; τ= -0.320).

Some adverse events (headache, nausea, dizziness) were reported equally in both groups. All patients underwent laboratory testing to exclude other causes of the symptoms. However, no participants were excluded.

Thus, the use of melatoninergic antidepressants, specifically agomelatine, in epilepsy patients showed clinical effectiveness in reducing the severity of affective symptoms and sleep disorders. Agomelatine was more effective than the SSRI antidepressant in reducing symptoms of anxiety and sleep disturbances. An interesting finding was the negative correlation between the number of antiepileptic drugs used and the level of depression. It is possible that underestimation of concomitant therapy influenced the study results. The main limitations of the study were as follows: the lack of verification of comorbid mental disorders according to ICD-10 or DSM-5, the severity of epilepsy and the influence of concomitant antiepileptic therapy, insufficient information on the doses of antidepressants and antiepileptic drugs taken. Therefore, bias in the following domains may have affected the study results: confounding factors, participant selection, potential deviation from the planned intervention, missing data, and outcome assessment.

Current research is more focused on determining the impact of antidepressants on the neurological aspect of epilepsy (frequency and severity of seizures). A promising direction is the study of comorbid conditions within the biopsychosocial paradigm.

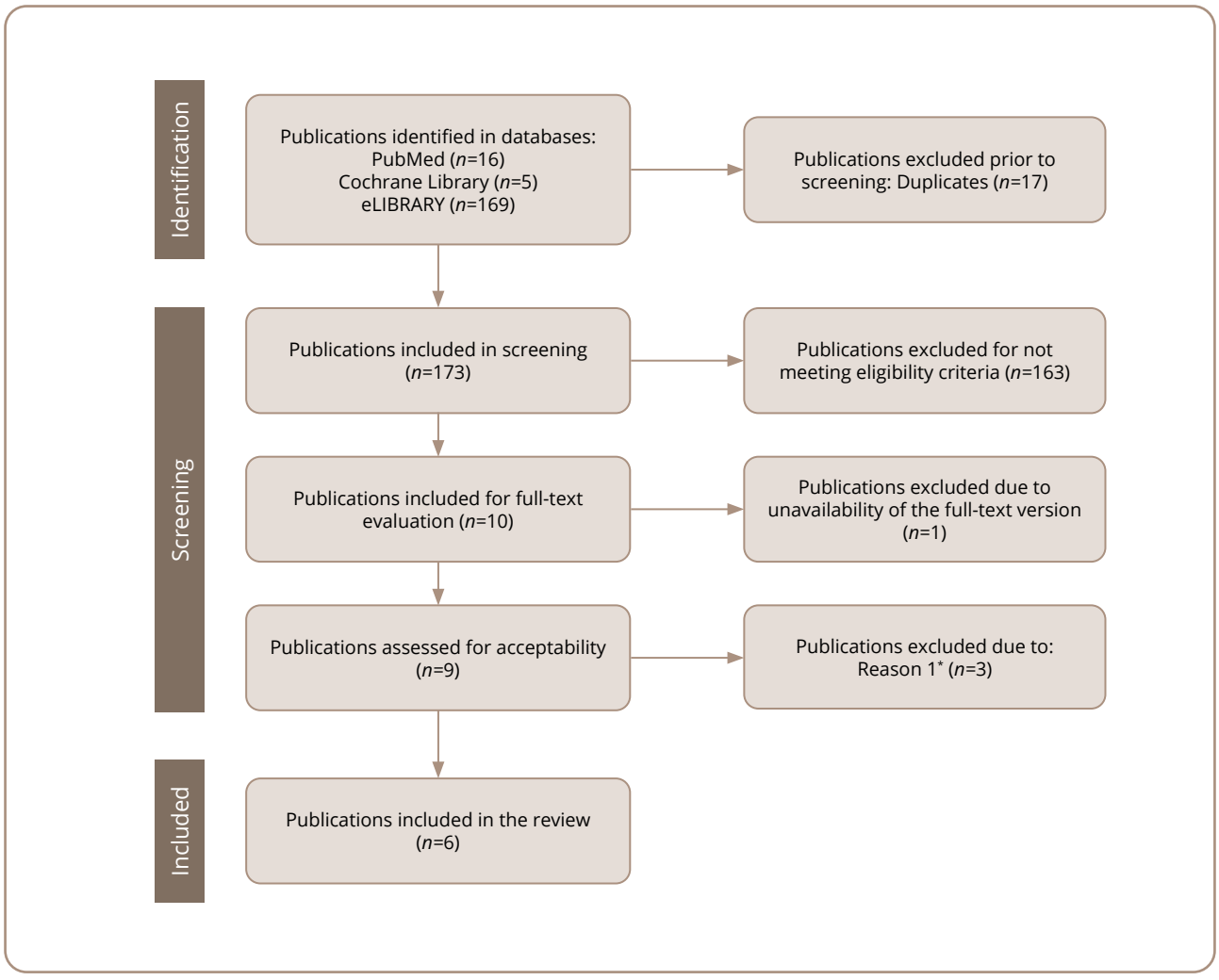


Figure 4. Flow chart demonstrating the selection process of comorbid depression and Parkinson's disease studies.

Note: * — did not meet eligibility criteria (diagnosis, publication type).

Source: Klimanova et al., 2024

Comorbid depression and Parkinson's disease

Based on the search algorithm, 190 publications were identified, of which 17 were excluded, and 173 were thoroughly reviewed. The study selection algorithm for the systematic review is shown in the flowchart (Figure 4).

Based on the eligibility criteria used in this review, a search was conducted for articles on recurrent depressive disorder comorbid with PD. However, no original clinical studies fully meeting the search parameters were found. Several studies evaluated the effectiveness of antidepressants affecting the melatoninergic neurotransmission (agomelatine and fluvoxamine) in depressive states in patients with PD. In three cases, the authors of the published articles were contacted for clarification of the study methodology. In the work by Fedorova et al. [134], it is noted that the sample consisted of "35 patients with PD with affective disorders and sleep disturbances", but the specific depressive disorders included were not specified.

Thus, for further review, 6 articles were selected: 3 clinical studies without a control group [135–137], one study with a control group (without treatment) [134], and two systematic reviews [81, 107]. The main characteristics of the selected experimental articles are provided in Table S4 in the Supplementary.

It should be noted that in all four selected clinical studies, agomelatine was used as the antidepressant. All included studies were open-label, prospective studies. The only two-arm study [134] examined the effectiveness of agomelatine compared to a group of patients who did not receive an antidepressant (the groups were comparable in terms of

sex, age, and severity of PD). In one study, participants were followed for six months [135]; in another, for two months [137], and in the remaining studies, participants were followed for 6 and 4 weeks, respectively [134, 136].

A total of 117 participants were included in the studies. The mean number of participants in the studies was about 29, with a minimum sample size of 18 [137] and a maximum of 40 participants [136]. The mean age of participants in one study was 75.2±8.3 years [135], while in the other three studies, it was lower: 65.5±12.5 years, 65.0±6.5 years, and 63±1.9 years, respectively [134, 136, 137].

The diagnosis of depression was made according to the DSM-4 criteria [135, 136]. In the study by Fedorova et al. [134], the US National Institute of Neurological Disorders and Stroke (NINDS) guidelines were used to diagnose depression in PD: the presence of at least one of the following two symptoms for a minimum of two weeks (low mood and/or loss of interest in or pleasure from life events). Additionally, patients with PD were required to have four or five additional symptoms, along with the two primary symptoms (sleep disturbances, low self-esteem; feeling of guilt, self-deprecation; tendency towards self-blaming for past events; bleak, pessimistic view of the future; increased fatigue, decreased concentration, and decision-making ability; significant fluctuation in appetite; psychomotor retardation, suicidal ideation, and recurrent thoughts of death) [138]. In one study [137], diagnostic criteria were not specified but it was noted that patients with "PD and moderate depressive disorders" were included. The criteria for diagnosing PD were described in only one study [133].

The results of a study of the efficacy of the antidepressant in the treatment were presented as continuous data, such as the mean score or mean score change on standardized rating scales. In all studies, complete data on the total number of dropouts were provided, including those due to adverse effects. However, in one study, the level of statistical significance of the results was not indicated [136].

As a secondary outcome measure, most studies assessed sleep quality using scales and questionnaires. However, only one study [135] used an objective method for sleep assessment, in particular video polysomnography (XLTEK EEG, NatusNeurology). The study by Gustov et al. [137] did not specify the method used to assess the severity of sleep disturbances. Only two studies assessed the severity of affective disturbances [134, 137].

The quality of the included studies was assessed independently by two authors (YYV and KYV) using the Cochrane Risk of Bias in Non-randomized Studies of Interventions [113].

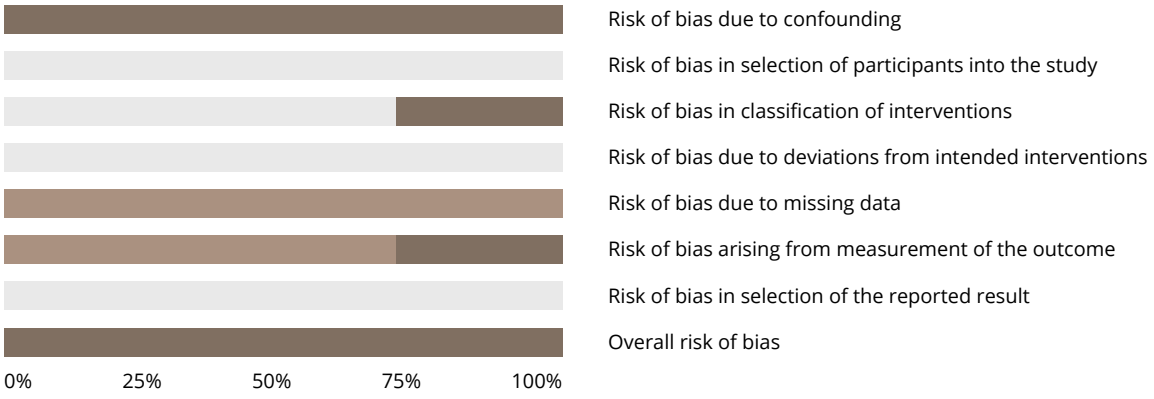
In the study with a control group [134], the randomization procedures and participant allocation were not specified, so we assessed the risk of bias as for non-randomized studies. We found the methodological quality of the included studies to be low (Figure 5).

Overall, the risk of bias in the reviewed studies can be considered high. In all the studies, the methods for addressing missing data were not specified, leading to a moderate risk assessment. The risk of bias in outcome measurement was rated as moderate in three studies, as bias may arise when outcome assessors are aware of the intervention status. In one study [137], the "Hospital Anxiety and Depression Scale" (HADS) was used, which relies on subjective patient self-assessment, resulting in a high-risk rating.

A significant reduction in depressive symptoms was observed during treatment with agomelatine in all the studies (Table S1 in the Supplementary). Improvements in sleep parameters were also reported in three studies [134, 135, 137], based on various scales and questionnaires. In one study [135], video polysomnography data showed improvements in periodic limb movement indices and a reduction in the number of awakenings (p <0.005 and p <0.05, respectively). Improvements in daily activities and quality of life were demonstrated in the studies by Avila et al. [135] and Fedorova et al. [134], respectively. A significant reduction in anxiety symptoms was reported in two studies [134, 137]; and in apathy, in one study [134]. Given that significant changes in Parkinson's disease motor symptoms (based on UPDRS Part III) during agomelatine treatment were observed in only one study [28], drawing definitive conclusions about the treatment efficacy remains premature.

The most commonly reported side effects of agomelatine included constipation, nausea, dizziness, headaches, and rash [135]. Notably, in only one study [135] did three patients withdraw from treatment after 12 weeks: two due to side effects (rash, nausea, headache, and dizziness) and one due to delirium. This study had the longest observation period (6 months) and the widest dose range (25–50 mg). In another study [134], only two patients experienced mild transient headaches at the start of treatment, which did not prevent them from continuing therapy. No significant adverse effects were reported in the studies by Golubev et al. [136] and Gustov et al. [137], both of which used a daily

A. Risk of bias graph



B. Risk of bias summary for each included study

Studies	D1	D2	D3	D4	D5	D6	D7	Overall
Avila et al. 2015	×	+	+	+	-	-	+	×
Fedorova et al. 2015	×	+	+	+	-	-	+	×
Golubev et al. 2014	×	+	+	+	-	-	+	×
Gustov et al. 2015	×	+	×	+	-	×	+	×

high moderate low

Figure 5. Assessment of risk of bias in non-randomized studies according to Cochrane guidelines.

Note: D1— Risk of bias due to confounding; D2 — Risk of bias in selection of participants into the study; D3 — Risk of bias in classification of interventions; D4 — Risk of bias due to deviations from intended interventions; D5 — Risk of bias due to missing data; D6 — Risk of bias arising from measurement of the outcome; D7 — Risk of bias in selection of the reported result; Overall — Overall risk of bias.

Source: Klimanova et al., 2024

dose of 25 mg of agomelatine. Furthermore, Golubev et al. [136] emphasized the absence of nausea, vomiting, increased constipation, urinary disorders, weight loss, reduced sexual function, or dizziness, which are important for this nosologic group.

In 2003, two systematic reviews assessed the efficacy and safety of antidepressant therapy in idiopathic PD [81, 106]. While the findings of these reviews were similar, only one of the three included studies focused on comparing fluvoxamine with amitriptyline [139]. Unfortunately, the detailed results were not available in the abstract and the full-text version could not be accessed.

The limitations of the aforementioned studies stem from the small number of published works meeting quality criteria, heterogeneity, and, in many cases, small sample sizes. This heterogeneity is due to the varying severity and intensity of comorbid depressive symptoms, as well as the differences in the dose and duration of treatment.

DISCUSSION

This work aimed to provide a systematic review of studies on the use of melatoninergic drugs (fluvoxamine and agomelatine) for treating depression comorbid with alcohol abuse, anxiety disorders (phobic anxiety, panic, and generalized anxiety disorder), and neuropsychiatric diseases (epilepsy, Parkinson's disease). The study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [107]. The search was performed in the scientific databases PubMed, Cochrane Library, and eLIBRARY. The search algorithm

was preregistered in the PROSPERO system (registration number #CRD42024536658).

The results of this systematic review confirm that, despite the high prevalence of depression comorbid with other mental and neurological disorders (ranging from 36.7% to 73.5%), the number of studies on the use of melatoninergic antidepressants remains extremely limited. For three out of the four comorbid conditions under review, the systematic literature search yielded no results, constituting what is termed an "empty review" in Cochrane terminology [140]. Given that this study aimed to review available data on the basis of which it could be possible to create clinical guidelines for the use of melatoninergic antidepressants in conditions comorbid with recurrent depressive disorder, as well as to identify research gaps and future directions for investigation, other types of systematic reviews (e.g., scoping reviews) were deemed less appropriate for this work [141, 142]. Broadening the search criteria to include more articles could have significantly shifted the focus point of the work. For example, adding "depressive episode" combined with alcohol abuse to the search parameters, in addition to recurrent depressive disorder, would lead to the inclusion of studies with patient samples that have comorbid disorders and those experiencing depressive states as part of substance withdrawal syndrome; i.e., without true comorbid conditions. Therefore, the preliminary conclusions regarding the efficacy of melatoninergic antidepressants in three comorbid conditions (recurrent depression with alcohol abuse, anxiety disorders, and epilepsy) were drawn based on studies involving participant groups with various affective disorders or affective disorders other than recurrent depressive disorder. As a result, these studies did not meet the predefined eligibility criteria.

The study results indicate that the use of fluvoxamine and agomelatine in alcohol abuse may be effective in reducing depressive symptoms, sleep disturbances, and cravings for alcohol. It is noteworthy, however, that more studies on the efficacy of fluvoxamine were identified compared to agomelatine. Some studies indicated the possibility of potential adverse effects, such as increased liver enzyme levels, associated with the concurrent use of agomelatine and alcohol abuse. In contrast, no significant adverse effects were reported with fluvoxamine. In addition, the use of pharmacogenetic testing to develop guidelines on drug selection and doses significantly enhances the effectiveness of fluvoxamine treatment. However, due to the limited number of studies specifically addressing comorbid depression and alcohol abuse, it is currently not possible to draw definitive conclusions about the efficacy and safety of these medications.

The results of this systematic review on the use of melatoninergic antidepressants in patient groups with depressive and anxiety symptoms suggest their potential efficacy in reducing anxiety, depression, anhedonia, sleep disturbances, and improving the quality of life, reducing the severity of mental disorders, and decreasing suicidal ideation. However, the review also highlights the lack of clinical data and specific treatment guidelines for individuals with comorbid depression and anxiety disorders.

The evaluation of existing studies on comorbid depression and epilepsy indicates that most of the research has focused on determining the impact of antidepressants on the neurological aspect of epilepsy (frequency and severity of seizures). In the only available study examining the use of agomelatine in patients with epilepsy and mixed affective states (depressive and anxiety symptoms and sleep disturbances), agomelatine demonstrated greater efficacy in reducing anxiety and sleep disturbances compared to another antidepressant (escitalopram). Additionally, a negative correlation was identified between depression levels and the number of antiepileptic drugs taken. Given the limited number of studies and the heterogeneous nosologies in the study sample, it is currently not possible to draw definitive conclusions regarding the efficacy and safety of melatoninergic antidepressants in comorbid depression and epilepsy conditions.

A review of studies on the use of agomelatine in PD with comorbid affective disorders suggests that this medication may contribute to significant reduction in depressive symptoms, improvements in sleep parameters and periodic limb movement indices, a decreased number of awakenings, better daily functioning and quality of life, as well as reductions in anxiety and apathy. One study also reported changes in motor symptoms associated with PD. However, based on the reviewed studies, it is not possible to draw definitive conclusions about the efficacy and safety of agomelatine in comorbid depression and PD due to the limited number of high-quality published studies, the clinical heterogeneity of the affective disorders examined, small sample sizes that preclude a generalization of the results to the broader population, the variability in doses and treatment durations, and the lack of consistency in efficacy and safety assessment measures.

Limitations

This systematic review is the first effort to classify and summarize the available data on the use of antidepressants with melatoninergic mechianism of action for depression comorbid with other mental and neuropsychiatric disorders. Overall, the results suggest potential efficacy of these drugs in alleviating symptoms of comorbid conditions. However, the study has several limitations. Primarily, there is a noted lack of research in this field. For most of the comorbid conditions examined, no studies on the use of melatoninergic antidepressants were identified, leading to a reliance on studies addressing similar symptomatology. Consequently, preliminary conclusions were drawn based on studies excluded from the review. As a result, the authors highlighted significant gaps in the research on the pharmacological effects of melatoninergic antidepressants for the comorbid conditions under consideration but were unable to answer the question posed regarding the clinical effectiveness of their use. Furthermore, it should be noted that the reviewed studies often involved small groups of participants, rarely used controlled and randomized designs, included heterogeneous diagnostic samples, and varied in terms of dose and duration of medication interventions.

CONCLUSION

Given the high prevalence of comorbid conditions in depressive disorders and the difficulty in selecting effective pharmacological treatments, further investigation into the use of melatoninergic antidepressants could have both theoretical and practical significance. Future directions for research may include the development and conduct of randomized, double-blind clinical trials to study the use of antidepressants with a melatoninergic mechanism of action in depression comorbid with other disorders (alcohol abuse, anxiety disorders, epilepsy, Parkinson's disease).

OTHER

Registration and protocol

This systematic review was pre-registered in the PROSPERO system (registration number #CRD42024536658). The study protocol can be made available upon request.

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Supplementary data

Supplementary material to this article can be found in the online version:
Appendix S1: https://doi.org/10.17816/CP15560-145407
Table S1: https://doi.org/10.17816/CP15560-145408
Table S2: https://doi.org/10.17816/CP15560-145409
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REVIEW

Comparison of Immune and Systemic Inflammation Parameters in Patients with a Depressive Episode in Bipolar Disorder and Major Depressive Disorder: A Scoping Review

Сравнение показателей иммунной системы и системного воспаления у пациентов с депрессивным эпизодом при биполярном аффективном и рекуррентном депрессивном расстройствах: обзор предметного поля

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Review

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ABSTRACT

BACKGROUND: Many studies have aimed to investigate and compare immune system and systemic inflammation parameters in patients with bipolar disorder (BD) and major depressive disorder (MDD) suffering from a depressive episode. However, no systematic review of the results has been conducted so far.

AIM: The aim of this study was to conduct a scoping review of research studies comparing immune and systemic inflammation parameters in patients with BD and MDD during a depressive episode.

METHODS: The search for studies was conducted in the Medline and eLIBRARY databases for the period from January 1994 to December 2022. Open-access articles written in English and Russian were selected. The review included original studies that compared groups of patients with BD and MDD (diagnosed based on the DSM-IV, DSM-5, or ICD-10 criterion) by immune and systemic inflammation parameters (such as the counts, ratio, and functions of blood cells, erythrocyte sedimentation rate, concentrations of immunoglobulins, cytokines, acute phase proteins, complement components, and autoantibodies).

RESULTS: The review included 24 studies. Current depressive episodes in patients with BD were associated with higher concentrations of chemokines (C-C motif chemokine ligand 3 (CCL3), CCL4, CCL5, CCL11), platelet-derived growth factor B, and interleukin 9 (IL-9) (two studies in each case), whereas patients with MDD tended to have higher concentrations of soluble tumor necrosis factor receptor 1 and immunoglobulin G to oxidized low-density lipoproteins (two studies each). Patients with BD and MDD had comparable concentrations of IL-8 (five studies); IL-2 and IL-10 (four

studies each); IL-13 and gamma interferon (three studies each); IL-17, IL-1Rα, the vascular endothelial growth factor, as well as white blood cells, monocyte, and platelet counts (two studies each). Contradictory results were obtained for the levels of tumor necrosis factor-α (the concentrations did not differ in five studies, were elevated in BD patients in five studies, were elevated in MDD patients in two studies), IL-6 (the concentrations did not differ in eight studies and were elevated in BD patients in four studies), C-reactive protein (the concentrations did not differ in six studies, were elevated in BD patients in two studies), IL-4 (the concentrations did not differ in three studies and were elevated in MDD patients in two studies), IL-1β and the neutrophil count (the levels did not differ in one study each and were elevated in BD patients in two studies). Several studies have demonstrated an association between immune and systemic inflammation parameters and the severity of depressive and anxiety symptoms, melancholic depression, age of mood disorder onset, body mass index, and imipramine equivalent.

CONCLUSION: Some immune and systemic inflammation parameters are associated with a current depressive episode in patients with MDD or BD. These parameters may be considered as potential biomarkers for a differential diagnosis of these disorders.

АННОТАЦИЯ

ВВЕДЕНИЕ: Многие исследования ставили задачей изучение и сравнение показателей иммунной системы и системного воспаления при депрессивных эпизодах у пациентов с биполярным аффективным расстройством (БАР) и рекуррентным депрессивным расстройством (РДР). Однако систематическое обобщение их результатов до настоящего времени не проводилось.

ЦЕЛЬ: Провести обзор предметного поля исследований, в которых сравнивали показатели иммунной системы и системного воспаления при текущем депрессивном эпизоде у пациентов с БАР и РДР.

МЕТОДЫ: Поиск исследований проводился в базах данных Medline и eLIBRARY (статьи на русском языке) за период с января 1994 г. по декабрь 2022 г. Отбирались статьи в открытом доступе, написанные на английском и русском языках. В обзор были включены оригинальные исследования, в которых сравнивали группы пациентов с текущим депрессивным эпизодом при БАР и РДР (диагнозы установлены по критериям DSM-IV, DSM-5 или МКБ-10) по показателям иммунной системы и системного воспаления (количество, соотношение и функции клеток крови, скорость оседания эритроцитов, концентрации иммуноглобулинов, цитокинов, белков острой фазы воспаления, компонентов комплемента, аутоантител).

РЕЗУЛЬТАТЫ: В обзор включено 24 исследования. С текущим депрессивным эпизодом при БАР ассоциированы более высокие концентрации хемокинов (C-C motif chemokine ligand 3 (CCL3), CCL4, CCL5, CCL11), тромбоцитарного фактора роста B, интерлейкина 9 (ИЛ-9) (по 2 исследования в каждом случае), при РДР — более высокие концентрации растворимого рецептора фактора некроза опухоли 1 и иммуноглобулинов класса G к окисленным липопротеинам низкой плотности (по 2 исследования). Пациенты с БАР и РДР имели сопоставимые концентрации ИЛ-8 (5 исследований); ИЛ-2 и ИЛ-10 (по 4 исследования); ИЛ-13 и интерферона гамма (по 3 исследования); ИЛ-17, ИЛ-1Rα, фактора роста эндотелия сосудов, а также количество лейкоцитов, моноцитов и тромбоцитов (по 2 исследования). Противоречивые результаты были получены для фактора некроза опухоли α (концентрации не различались в 5 исследованиях, повышены при БАР в 5, повышены при РДР в 2), ИЛ-6 (концентрации не различались в 8 исследованиях, повышены при БАР в 4), С-реактивного белка (концентрации не различались в 6 исследованиях, повышены при БАР в 2), ИЛ-4 (концентрации не различались в 3 исследованиях, повышены при РДР в 2), ИЛ-1β и количества нейтрофилов (не различались по 1 исследованию, повышены при БАР в 2). В нескольких исследованиях была обнаружена ассоциация показателей иммунной системы и системного воспаления с тяжестью депрессивной и тревожной симптоматики, меланхолическим подтипом депрессии, возрастом дебюта расстройства настроения, индексом массы тела и имипраминовым эквивалентом.

ЗАКЛЮЧЕНИЕ: Ряд показателей иммунной системы и системного воспаления ассоциирован с текущим депрессивным эпизодом у пациентов с РДР или БАР. Эти показатели могут быть рассмотрены в качестве потенциальных биомаркеров для дифференциальной диагностики указанных расстройств.

Keywords: *depressive episode; bipolar disorder; major depressive disorder; differential diagnosis; immune system; inflammation*

Ключевые слова: *депрессивный эпизод; биполярное аффективное расстройство; рекуррентное депрессивное расстройство; дифференциальная диагностика; иммунная система; воспаление*

INTRODUCTION

The role of inflammation and immune system disorders in the pathogenesis of depression has been studied for several decades [1, 2]. As a result, numerous clinical findings have confirmed the connection between neuroinflammation and the development of depression [3, 4]. Additionally, patients with depression have been found to have high concentrations of interleukin-6 (IL) and the C-reactive protein (CRP) [5, 6], to show signs of microglial activation [7] and increased levels of kynurenine associated with the effect of the neuroinflammation on serotonin synthesis [4]. It has also been shown that the pro-inflammatory cytokine interferon (IFN) α induces depression as a side effect [8, 9]. Moreover, patients who received higher doses of IFNα for 24 weeks showed more severe depressive symptoms [9]. In contrast, it appears that some drugs with anti-inflammatory activity may also have antidepressant effects [4]. The antidepressant effect has also been studied in nonsteroidal anti-inflammatory drugs, cytokine inhibitors, statins, polyunsaturated fatty acids, and corticosteroids, but the results have been contradictory [10].

Some authors critically evaluate the formal diagnostic approach (based on Diagnostic and Statistical Manual of Mental Disorders, DSM and the International Classification of Diseases, ICD) to the verification of depression in major depressive disorder (MDD) and bipolar disorder (BD), considering their pathogenetic and clinical features [11]. In patients with BD, the final diagnosis is usually made 6–8 years after the first affective phases [12]. The most common incorrect diagnosis is MDD, which is related to the typical onset of BD with depressive phases and the delayed onset of hypo/manic phases or difficulties in retrospectively verifying them [13]. As a result, antidepressants are often mistakenly prescribed for the treatment of the current depressive episode, leading to pharmacogenetic phase inversions and the development of mixed episodes and rapid cycling in patients with BD [14].

It seems logical to consider the differences in the pathogenesis of depression in MDD and BD [15, 16]. In this regard, molecular, genetic, and neuroimaging studies of specific markers that can differentiate depressive episodes in BD and MDD on a neurobiological basis are highly relevant [17]. Studies of immunological markers in peripheral blood in BD and MDD have revealed disruptions in immune response regulation [18, 19]. It is suggested that these markers could be used to improve the accuracy of the differential diagnosis of BD and MDD [20].

However, there is a lack of studies on the specific immune system and systemic inflammation markers that compare current depression in BD and MDD, especially in conjunction with clinical manifestations and disorder course features. These findings are crucial for further understanding whether both phenotypes are biologically continuous conditions within the same spectrum of pathophysiological changes, or whether BD and MDD are independent conditions with different pathophysiological bases [21–23]. Comparison of immune system and systemic inflammation markers in depression in patients with MDD and BD is necessary for identifying the biomarkers of these disorders, finding new psychopharmacological targets, and predicting the effectiveness of the standard treatment for BD and MDD.

To our knowledge, scoping reviews, systematic reviews, and meta-analyses comparing immune system and systemic inflammation markers in a current depressive episode in patients with BD and MDD have not been conducted. On this basis, we conducted a systematic literature analysis using the scoping review methodology to describe and summarize the results of these studies.

METHODS

The description of the review was carried out in accordance with the recommendations (checklist of control questions) from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, modified for scoping

reviews [24]. The protocol for this study has not been registered in public sources. The protocol can be obtained by sending a justified request to the corresponding author.

Eligibility criteria

Inclusion criteria:

The review included articles published in peer-reviewed journals in English or Russian, containing the results of studies on patient groups with current depressive episodes in MDD and BD (type I or II), comparing immune system and systemic inflammation markers (immunoglobulins (Ig) A, M, G, and E, autoantibodies, cytokines, complement components, acute-phase proteins, growth factors, erythrocyte sedimentation rate, blood cell counts, ratios, and functions). Diagnosis of MDD and BD was based on the criteria of the DSM-IV, DSM-5 or the ICD-10.

Exclusion criteria:

- Case report studies.
- Full or partial data duplication (in the case of partial duplication, the publications with the largest sample size were included in the review).
- Absence of mean or median values for immune system and systemic inflammation markers and/or results of statistical comparisons between the patient groups with BD and MDD.
- Studies that have analyzed mixed patient groups (including patients with dysthymia, cyclothymia, schizophrenia spectrum disorders).
- The article with the research results is behind a paywall or the author did not grant access upon request.

Information sources

The search was conducted in the electronic databases Medline and eLIBRARY. The search period covered ran from January 1994 to December 2022. The search was limited to 1994, because that year marked the release of DSM-IV, which contained the first description of the diagnostic criteria for BD II. The search was carried out in December 2023.

Search strategy

The search query in the Medline database included the following combination of keywords and search operators: [(unipolar depression) OR (major depressive disorder) OR (recurrent depressive disorder)] AND [(bipolar depression) OR (bipolar disorder) OR (bipolar affective disorder) OR (bipolar disorder I type) OR (bipolar disorder II type)] AND [(immunological alterations) OR (immunomarkers) OR (immunological markers) OR (immunological) OR (immune-inflammatory profiles) OR (cytokines) OR (immunity) OR (neuroinflammation) OR (inflammation) OR (immune system)]. The search query in Russian in the eLIBRARY database included: [(unipolar depression) OR (major depressive disorder) OR (recurrent depressive disorder)] AND [(bipolar depression) OR (bipolar disorder) OR (bipolar affective disorder) OR (bipolar I disorder) OR (bipolar II disorder)] AND [(immunological alterations) OR (immunomarkers) OR (immunological markers) OR (immunological) OR (immune-inflammatory profiles) OR (cytokines) OR (immunity) OR (neuroinflammation) OR (inflammation) OR (immune system)]. The search query was formulated by (AK) and approved by all co-authors. When searching the Medline electronic database, additional time filters, as mentioned above, were used. When searching in the eLIBRARY database, the following filters were applied: search by title and abstract; publication type: journal article.

Selection process

The primary screening of potentially relevant articles was conducted by reviewing their titles and abstracts and performing a preliminary assessment if they meet the eligibility criteria. The selected articles were listed for further review of their full texts and selection of relevant studies that met all the planned inclusion and exclusion criteria. The screening and content review of the articles were performed (AK) and confirmed by two other authors of the review (PS, NP). The final decision in case of disagreements regarding the included articles was made by one author (NP).

Data extraction

A standardized form in the format of an electronic spreadsheet was used for data extraction. The following data were extracted from the relevant (selection criteria-compliant) articles: title, authors, year of publication, country, study design, patient sample size, biological material, study method, immune system and systemic inflammation markers, drug therapy at the time of participation in the study, and group comparison results considering sex or type of BD. Data were extracted by one author (AK) and then double-checked and confirmed by the other authors of the review (PS, OL, and NP). Disagreements were resolved by one author (NP).

Critical assessment

No critical assessment of the sources included in the review was conducted.

Analysis of results

A descriptive analysis of the selected sources was performed. The results of the comparison of the BD and MDD groups based on immune system markers and systemic inflammation values in each study were described using categories such as "Higher in BD" and "Higher in MDD" if differences were statistically confirmed, and "No differences" if no significant differences were found. We also analyzed the relationship between immune system markers, systemic inflammation, and various clinical characteristics of depressive episodes in BD and MDD found in the included studies.

RESULTS

Source selection

As a result of the database search, 710 articles were netted, all in Medline. After reviewing the titles and abstracts, 143 articles were deemed potentially relevant, of which 126 were publicly available or provided by the authors. After reading the full texts of the articles, 24 original studies that met the eligibility criteria were included in the final analysis (Figure 1) [18, 20, 25–46].

Characteristics of the sources

A total of 2,785 patients with BD and 10,944 patients with MDD participated in 24 studies included in the review. The studies were published between 2007 and 2022. Of the 24 studies, 20 used a cross-sectional design, while the remaining four employed different approaches: cohort

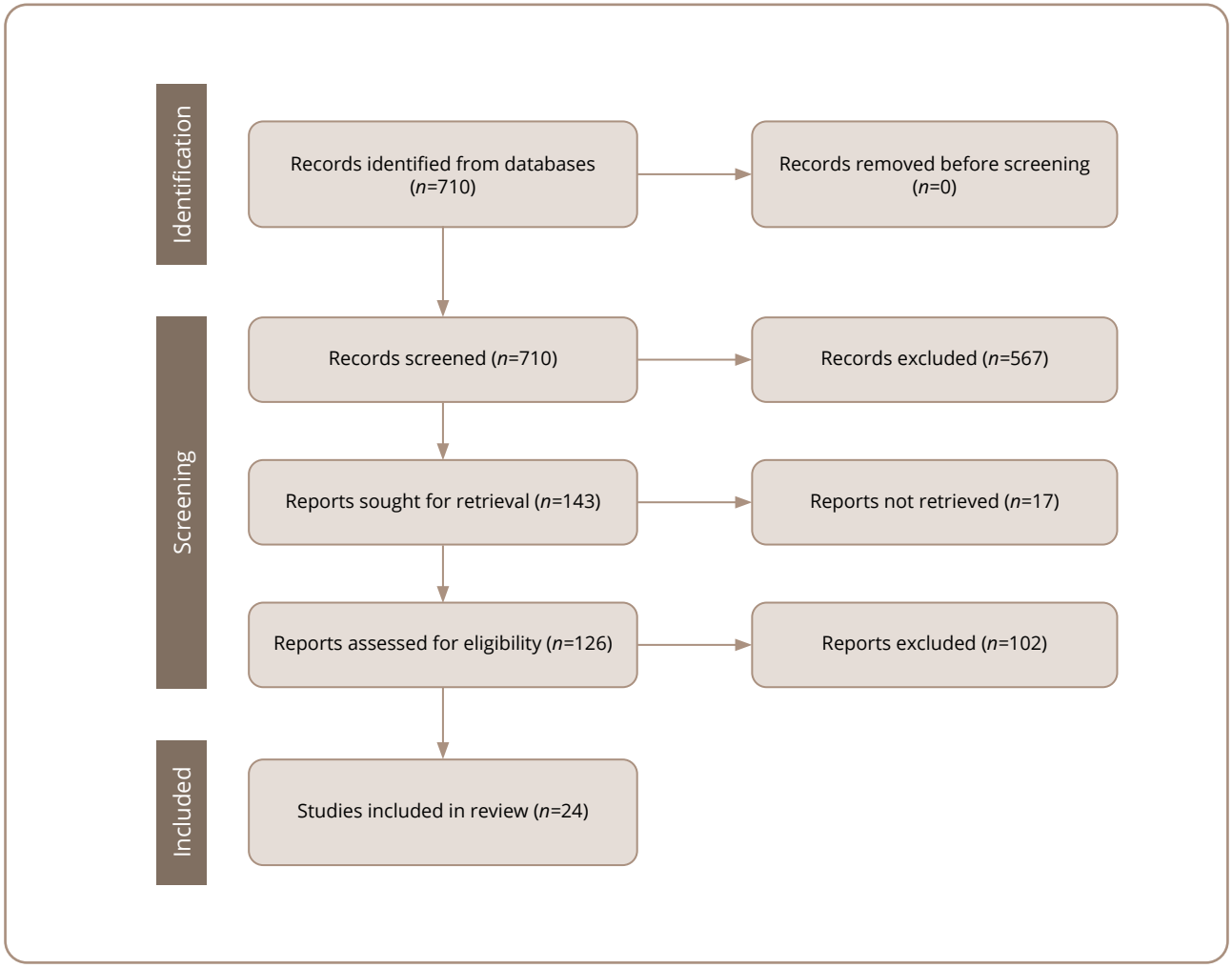

Figure 1. PRISMA flow chart of the literature search and the selection process.

Source: Kasyanova et al., 2024.

studies (*n*=2), case-control studies (*n*=1), and a double-blind placebo-controlled study (*n*=1). Most studies were conducted by authors from Europe (Italy — four studies, Bulgaria — three, Belgium — two, Turkey — two; Romania, Poland, Germany, Netherlands — one each), Asia (China — five studies; Taiwan — four; Thailand — three), and North America (Canada and the USA — four studies each). Additionally, three studies were conducted by authors from Australia, and one from Brazil. No studies in Russian that met the inclusion criteria were identified.

Results of studies

Table 1 presents the results of the comparison of immune system and systemic inflammation markers during a current depressive episode in patients with BD and MDD. Promising markers of the current depressive episode in BD include chemokines (C-C motif chemokine ligand 3 (CCL3), CCL4, CCL5, CCL11), platelet-derived growth factor B (PDGFB), and IL-9 (with two confirming studies for each). In MDD, promising markers include soluble tumor necrosis factor receptor 1 (sTNFR1) and IgG to oxidized low-density lipoproteins (LDL) (with two studies for each). Patients with BD and MDD had comparable concentrations of IL-8 (reported in five studies), IL-2 and IL-10 (in 4 studies), IL-13 and IFN-γ (in three studies); IL-17, IL-1Rα, vascular endothelial growth factor, leukocyte, monocyte, and platelet counts (in two studies). Contradictory results were obtained for TNF-α (no differences found in five studies, increased level in BD in five, increased level in MDD in two), IL-6 (no differences found in 8 studies, increased level in BD in four), CRP (no differences found in six studies, increased level in BD in two), IL-4 (no differences found in three studies, increased level in MDD in two), IL-1β, and neutrophils (no differences found in one study, increased level in BD in two).

The type of BD was considered in three studies when analyzing immune system and systemic inflammation markers. In the study by Brunoni et al. [18], no differences in the studied markers (IL-6, TNF-α, sTNFR2, etc.) were found between patients with BD I and II. The study by Simeonova et al. [33] found that in BD I, compared to BD II, the total concentrations of IgM to NO adducts, lipopolysaccharide (LPS) of *Morganella morganii* and *Citrobacter koseri*, IgA to LPS of *Pseudomonas putida* and *Citrobacter koseri*, and the integral index ratio of IgM/IgA to LPS of all Gram-negative bacteria were higher. Higher concentrations of IgM and IgA to LPS of Gram-negative bacteria in BD I were also found in a third study [34].

The biological sex of patients was also considered in three studies when analyzing immune system and systemic inflammation markers. The study by Wei et al. [26] showed that in patients with MDD, neutrophil and lymphocyte counts were higher in men compared to women. In patients with BD, neutrophil and lymphocyte counts in men were also higher, while platelet counts were lower than in women [26]. In the study by Lu et al. [35], it was found that in patients with MDD and BD during depressive episodes, the concentration of IL-8 in serum was higher in men than in women. In the study by Becking et al. [43], no statistically significant differences were found in the concentrations of TNF-α, IL-6, and CRP when comparing men with MDD and BD, as well as separately comparing women with MDD and BD. Comparison of immune system and systemic inflammation marker values between men and women was not performed in this study.

In patients with MDD and BD, positive correlations were found between various immune system and systemic inflammation markers and the severity of depressive and anxiety symptoms, the melancholic subtype of depression, age of onset of mood disorder, and the body mass index (Table 2). Negative correlations were also observed between various immune system and systemic inflammation markers and the imipramine equivalent and the level of anxiety symptoms in both patient groups.

DISCUSSION

Key findings

For the first time, the results of original studies investigating immune system and systemic inflammation markers in current depression among patients with MDD and BD were summarized. The data related to the most commonly investigated immune system and systemic inflammation markers (IL-1β, IL-4, IL-6, TNF-α, CRP, neutrophil count) are contradictory. Differences in the concentrations of IL-2, IL-8, IL-10, IL-13, IFN-γ, IL-17, IL-1Rα, vascular endothelial growth factor, leukocyte, monocyte, and platelet counts in patients with BD or MDD were not identified in any of the studies. However, promising biomarkers for the differential diagnosis of a current depressive episode were shown to include chemokines (CCL3, CCL4, CCL5, CCL1), PDGFB, IL-9 (higher concentrations in BD), as well as sTNFR1 and IgG to LDL (higher concentrations in MDD). Several studies have identified associations between immune system and systemic inflammation markers and the clinical characteristics of the mood disorders under investigation.

Table 1. Study of immune system and systemic inflammation markers during depressive episode in patients with bipolar disorder and major depressive disorder

Source	Country	Study design	Sample size, abs.		Biomaterial (study method)	Therapy*	Indicators higher in BD	Indicators higher in MDD	No differences (BD vs MDD)
			BD	MDD					
Comai et al., 2022 [25]	Italy, Canada	Cross-sectional**	66	100	Plasma (multiplex assay)	Yes	IL-1β, IL-2, IL-6, IL-9, CCL11, CCL3, PDGF-B, CCL4, CCL5, TNF-α	IL-4, IL-7	IL-1Rα, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, IFN-γ, MCP-1 (CCL2), CXCL10, FGF, G-CSF, GM-CSF, VEGF
Wei et al., 2022 [26]	China	Cross-sectional	1,664	8,899	Whole blood (blood chemistry)	No data	MPV, neutrophils, lymphocytes	Platelets, RDW, PLR, PAR	PDW, PCT, RPR
Bulut et al., 2021 [27]	Turkey	Cross-sectional**	70	93	Whole blood (blood chemistry)	No data	Not detected	Not detected	NLR, PLR
Caldirola et al., 2021 [28]	Italy	Cross-sectional	135	156	Serum (ELISA)	Yes	CRP (> 3 and ≤ 10 mg/L)	Not detected	Not determined
Dionisie et al., 2021 [29]	Romania	Cross-sectional	34	83	Whole blood (blood chemistry, complete blood count)	Yes	Neutrophils, NLR, SII	Lymphocytes	White blood cells, monocytes, platelets, PLR, MLR
Huang et al., 2021 [30]	Taiwan	Cross-sectional**	33	66	Serum (ELISA)	Yes	TNF-α, IL-6	Not detected	CRP, IL-2, MCP-1 (CCL2), P-selectin
Karadağ et al., 2021 [31]	Turkey	Cross-sectional	31	25	Serum (ELISA)	Yes	Not detected	Not detected	TRAIL, TWEAK, CRP
Poletti et al., 2021 [32]	Italy	Cross-sectional**	81	127	Plasma (multiplex assay)	Yes	IL-1β, IL-9, IL-16, TNF-α, MIF, CCL1, MCP-1 (CCL2), CCL3, CCL4, CCL5, CCL8, CCL11, CCL13, CCL21, CCL22, CCL25, CCL26, CCL27, CXCL1, CXCL6 , CXCL9, CXCL10, CXCL11, CXCL16, CX3CL1, bFGF, PDGF-B	Not detected	IL-1Rα, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, IL-17, CCL7, CCL15, CCL17, CCL19, CCL20, CCL23, CCL24 , CXCL2, CXCL5, CXCL8, CXCL12, CXCL13, VEGF
Brunoni et al., 2020 [18]	Brazil, USA, Thailand, Australia, Canada, Bulgaria	Cross-sectional	59	245	Plasma (ELISA, flow cytometry)	Patients with MDD – no, with BD – yes	IL-6, sTNFR2, IL-18, IL-33, sST2, klotho	IL-1β, TNF-α, sTNFR1, IL-12, IL-10	IL-8, IL-12p70
Simeonova et al., 2020, a [33]	Bulgaria, Belgium, Canada, Poland, Thailand, Australia	Cross-sectional**	66	44	Serum (ELISA, colorimetric assay)	Yes	IgA to LPS of *Pseudomonas putida* and *Citrobacter koseri*	IgG to oxidized LDL, IgM to LPS of *Hafnia alvei* (in comparison with BD II)	Total peroxides, IgM to LPS of *Morganella morganii, Pseudomonas aeruginosa, P. putida, C. koseri, Klebsiella pneumoniae*, IgA to LPS of *H. alvei, P. aeruginosa, M. morganii, K. pneumoniae*, total IgA/IgM to LPS of gram-negative bacteria
Simeonova et al., 2020, b [34]	Bulgaria, Belgium, Thailand, Australia	Cross-sectional**	54	47	Serum (ELISA, colorimetric assay)	Yes	Not detected	IgM to MDA, oleic acid, Pi, total IgM to OSEs, IgG to oxidized LDL (compared to BAR II); total peroxides (compared to BAR I)	IgM to LPS of *H. alvei, P. aeruginosa, M. morganii, P. putida, C. koseri, K. pneumoniae*, IgA to LPS of *H. alvei, P. aeruginosa, M. morganii, P. putida, C. koseri, K. pneumoniae*, IgM to azelaic acid, total IgM to NO adducts
Lu et al., 2019 [35]	China	Case control	26	21	Serum (ELISA, immunoturbidimetric assay)	No	Not detected	Not detected	IL-6, IL-8, CRP

Mazza et al., 2019 [36]	Italy	Cross-sectional	40	36	Whole blood (blood chemistry)	No data	Not detected	Not detected	Leukocytes, neutrophils, lymphocytes, monocytes, platelets, NLR, MLR, PLR
Mao et al., 2018 [20]	China	Cohort**	61	64	Plasma (multiplex assay)	Yes	TNF-α, IL-4 (after 12 weeks of treatment)	TNF-α and IL-13 before treatment, TNF-α and IL-4 after 12 weeks of treatment in patients who responded to treatment	IL-4, IL-6 (before treatment). IL-13, IL-6 (after 12 weeks of treatment in patients who responded to treatment)
Chang et al., 2017 [37]	Taiwan	Cohort**	88	72	Plasma (ELISA)	No	CRP	Not detected	Not detected
Hage et al., 2017 [38]	USA	Cross-sectional**	37	64	Plasma (ELISA)	Patients with MDD – no, with BD – yes	*ИЛ*-10, MCP-1 (CCL2)	CRP	TNF-α, IL-6, IL-8, IL-1β
Park et al., 2017 [39]	USA	Double-blind, placebo-controlled study	31	49	Plasma (multiplex assay)	Yes	TNF-α, IL-6, IL-8	sTNFR1 (higher at baseline, 230 min, and 1 day, but not 3 days after ketamine injection)	IFN-γ, IL-2, IL-5, IL-10
Ren et al., 2017 [40]	China	Cross-sectional**	30	30	Plasma (liquid chromatography with tandem mass spectrometry)	No	Alpha-1-acid glycoprotein, C-mannose receptor type 2, antileukoproteinase	Serotransferrin, pantetheinase, apolipoprotein A-I, endoglin, suprabasin, sulfhydryl oxidase	Not detected
Wu et al., 2017 [41]	China	Cross-sectional**	23	22	Whole blood, plasma (flow cytometry)	No	Not detected	CD3+CD8+ cytotoxic T cells	CD3+ T cells, CD3+CD4+ Th cells, CD3-CD16+CD5+ NK cells, TIM-3, PD-1, PD-L1, PD-L2, IFN-γ, TNF-α, IL-2, IL-4, IL-10, IL-6
Schaefer et al., 2016 [42]	Germany	Cross-sectional**	22	11	Serum (ELISA)	Yes	Not detected	Not detected	sICAM-1
Becking et al., 2015 [43]	Netherlands	Cross-sectional**	124	640	Plasma (ELISA)	No data	Not detected	Not detected	TNF-α, IL-6, CRP
Manalai et al., 2012 [44]	USA	Cross-sectional**	39	55	Serum (immunofluorescence assay)	Yes	Not detected	Not detected	IgE to tree and ragweed allergens (seropositive/seronegative status)
Su C et al., 2011 [45]	Taiwan	Cross-sectional**	10	18	Serum (ELISA), plasma (immunoturbidimetric assay)	No	Not detected	Not detected	CRP, TNF-α, IL-6
Hung et al., 2007 [46]	Taiwan	Cross-sectional**	15	21	Serum (ELISA), plasma (immunoturbidimetric assay)	No	Not detected	Not detected	CRP, TNF-α, IL-6

Note: * Participant's treatment at study entry; ** Design not specified in cited papers, determined by the authors of this review. bFGF — basic fibroblast growth factor; CCL11 — C-C motif chemokine ligand 11; CXCL10 — C-X-C motif chemokine ligand 10; FGF — fibroblast growth factor; IgA — immunoglobulin A; IgE — immunoglobulin E; IgG — immunoglobulin G; IgM — immunoglobulin M; MCP-1 — monocyte chemoattractant protein 1; MDA — malondialdehyde; MIF — macrophage migration inhibitory factor; MLR — monocyte-to-lymphocyte ratio; MPV — mean platelet volume; NLR — neutrophil-to-lymphocyte ratio; NK cells — natural killer cells; NO — nitric oxide; OSE — oxidation-specific epitopes; PAR — platelet-to-albumin ratio; PCT — plateletcrit; PD-1 — programmed cell death protein 1; PDGF-B — platelet-derived growth factor B; PD-L1 — programmed death-ligand 1; PDW — platelet distribution width; Pi — phosphatidylinositol; PLR — platelet-to-lymphocyte ratio; RDW — red cell distribution width; RPR — red cell distribution width-to-platelet ratio; sICAM-1 — soluble intercellular adhesion molecule-1; SII — systemic immune-inflammation index; sST2 — soluble suppression of tumorigenicity 2; sTNFR2 — soluble tumor necrosis factor receptor 2; Th cells — T-helper lymphocytes; TIM-3 — T-cell immunoglobulin and mucin-domain containing-3, immunoglobulin and mucin/mucin domain; TRAIL — TNF-related apoptosis-inducing ligand; TWEAK — TNF-like weak inducer of apoptosis; VEGF — vascular endothelial growth factor; BD — bipolar disorder; G-CSF — granulocyte colony-stimulating factor; GM-CSF — granulocyte-macrophage colony-stimulating factor; IL-1β — interleukin-1beta; IFN-γ — interferon gamma; ELISA — enzyme-linked immunosorbent assay; LDL — lipoproteins; LPS — lipopolysaccharide; MDD — major depressive disorder; CRP — C-reactive protein; TNF-α — tumor necrosis factor-α.

Table 2. The relationship between immune system and systemic inflammation markers and the clinical characteristics of depression in bipolar disorder and major depressive disorder

Clinical characteristic	Immune system and systemic inflammation markers	
	BD	MDD
Severity of depressive symptoms (positive relationship)	CRP [37], sTNFR1 [39], IgA to LPS of *Pseudomonas putida, Citrobacter koseri, Hafnia alvei, Pseudomonas aeruginosa, Morganella morganii, Klebsiella pneumoniae* [33], IgM to azelaic acid and oleic acids, MDA and Pi, total IgM to OSE [34], + CCL4 [25] in patients with MDD	–
Level of anxiety (positive relationship)	sTNFR1, sTNFR1/sTNFR2 ratio [18]	–
Level of anxiety (negative relationship)	sTNFR2 [18]	–
Severity of hypo/manic symptoms (positive relationship)	CRP [35]	Not determined
Age of disorder onset (negative relationship)	CD3+CD8+ cytotoxic T lymphocytes [41]	Not determined
Melancholic type of depression (positive association)	IgA to LPS of *C. koseri* [33]	IL-1β [18], IgA to LPS of *C. koseri* [33]
Anxiety as a personality trait (positive relationship)	sTNFR1, sTNFR1/sTNFR2 ratio [18]	–
Body mass index (positive relationship)	IL-1β [25], IL-5 [39], IL-6 [39]	–
Imipramine equivalents (negative relationship)	TNF-α [25], IL-9 [25], CCL4 [25], CCL5 [25]	–

Note: CCL11 — C-C motif chemokine ligand 11; IgA — immunoglobulin A; IgM — immunoglobulin M; MDA — malondialdehyde; OSE — oxidation-specific epitopes; Pi — phosphatidylinositol; sTNFR1 — soluble tumor necrosis factor receptor 1; TIM-3 — T-cell immunoglobulin and mucin-domain containing-3. BD — bipolar disorder; IL-1β — interleukin-1beta; LPS — lipopolysaccharide; MDD — major depressive disorder; CRP — C-reactive protein; TNF-α — tumor necrosis factor-α.

Limitations

The present review has several important limitations. First, the broad inclusion criteria meant that the studies reviewed had examined different components of immunity. Consequently, despite the number of included studies and the final sample size, some potentially interesting immune and systemic inflammation markers had been investigated in only a small number of studies. Second, although all the studies had excluded conditions that could influence immune and systemic inflammation marker levels, it is impossible to completely rule out this and other confounding factors because the included studies varied in how the authors accounted for comorbid conditions or excluded them (e.g., through clinical examination, patient self-reporting, or medical records). Third, in 14 (58%) of the 24 studies, immune system and systemic inflammation markers were assessed during ongoing pharmacotherapy for mental disorders, which could have affected the results [47]. Fourth, 17 out of 143 potentially relevant studies were unavailable as full-text articles and were therefore excluded from the review. As a result, potentially significant findings regarding the relationship between immune and systemic inflammation markers and depressive episodes in MDD or BD patients might have been overlooked. The original article search was conducted by a single author without reviewing the reference lists of the included papers, increasing the risk of missing relevant studies. Most of the studies included in this review were cross-sectional, making it impossible to infer causal relationships between immune and systemic inflammation markers and depressive episodes in MDD or BD patients.

Comparisons with existing literature

The numerous conflicting findings regarding the association of immune system and systemic inflammation markers with current depressive episodes in MDD and BD can be attributed to the challenges in the psychiatric classification of these disorders. Until 1980, both conditions were grouped under the manic-depressive disorders category, but some researchers now view them as two extremes of a bipolar spectrum [48, 49]. Given this, it is logical that MDD and BD share more similarities than differences. Nevertheless, even subtle distinctions can be crucial in terms of their differential diagnosis. Below, we present the available data on the immune system and systemic inflammation markers identified in this review as the most promising for distinguishing between major depressive disorder and bipolar disorder.

In relation to BD, changes in the concentrations of various cytokines have been the primary focus of previous research. However, the association of chemokines with this disorder has also been confirmed by the systematic reviews conducted by Stuart et al. [50] and Misiak et al. [51]. Chemokines are a family of cytokines capable of inducing directed migration (chemotaxis), particularly to sites of inflammation. All chemokines interact with transmembrane receptors linked to G-proteins, which are expressed, among other locations, within the vascular network of the blood-brain barrier [52]. The link between chemokines and mental disorders is mediated by their neuromodulatory and neurotransmitter-like effects, as well as their role in regulating neurogenesis [50, 51]. The effects of chemokines on the brain are complex, as these proteins exhibit both neuroprotective and neurotoxic properties [53]. Understanding the role of chemokines in the pathogenesis of BD may open new prospects for the development of therapeutic strategies aimed at modulating inflammatory processes and immune regulation.

PDGFB, a growth factor stored in platelet granules and released upon activation, plays a role in blood vessel formation, proliferation, and the migration of mesenchymal cells [54]. PDGF-mediated signaling has been shown to regulate various brain functions, including neurogenesis [55, 56]. Additionally, PDGF-BB inhibits the N-methyl-D-aspartate receptor (NMDAR)-mediated component of excitatory synaptic currents [57, 58], while glutamatergic neurotransmission via NMDAR is implicated in the pathophysiology of MDD and BD [58, 59]. Idemoto et al. [58] suggested that PDGF-BB might contribute to NMDAR dysfunction in mood disorders and mediate pathophysiological differences between MDD and BD. Serum PDGF-BB levels were found to be significantly lower in MDD groups during both depressive phase and euthymic state compared to BD groups and healthy controls. These findings suggest that serum PDGF-BB could be a potential biomarker for the differential diagnosis of BD and MDD. The authors hypothesize that decreased PDGF-BB levels in MDD may be linked to diminished neuroprotective activity and the activation of NMDAR-mediated excitotoxicity in the brain [58]. Several studies have also identified a relationship between PDGF-BB levels and the microstructure of white matter in depressive patients [25, 60, 61]. Moreover, Benedetti et al. [60] demonstrated an inverse relationship between cytokine and PDGF-BB levels and the integrity of myelin sheaths during demyelination [60]. White matter structural abnormalities are known to be associated with the risk of mood disorders, adverse childhood experiences, affective phases, and cognitive impairments in BD [25, 62, 63], as well as the duration of the disorder, treatment resistance, and depression severity in MDD [25, 64, 65].

IL-9 is a pleiotropic cytokine primarily produced by type 2 T-helper cells (Th2), as well as by Th17 cells, regulatory T cells (Treg), and a Th9 subpopulation [54]. This cytokine promotes survival and activates mast cells, epithelial cells, B cells, and T cells [54]. IL-9 may contribute to inflammatory diseases and serves as a key molecule in the differentiation of Th17 and regulation of Treg function [66]. The role of IL-9 in depression may involve its influence on glutamatergic transmission. Th17 cells, through IL-17, reduce the expression of glutamate transporters [67]. A recent study by Poletti et al. showed a positive correlation between IL-9 and glutamate concentrations in the brains of BD patients [53]. The same study also found that IL-1β and CCL5 were associated with higher concentrations of myo-inositol and N-acetylaspartate in the anterior cingulate cortex, respectively [53]. Thus, the impact of cytokines, including IL-1β and IL-9, on the pathogenesis of BD may be mediated through their involvement in neuroinflammatory processes, effects on neuroplasticity and brain metabolism, and their roles in neurotransmission and neurodegeneration.

High concentrations of TNF-α in patients with MDD have been confirmed by several meta-analyses [68, 69, 70] and an umbrella review [71]. TNF-α, a molecule of the innate immune system, is primarily produced by macrophages, natural killer cells, and T lymphocytes [54]. TNF exists in both transmembrane and soluble forms, functioning through binding to tumor necrosis factor receptors 1 and 2 (TNFR1 and TNFR2) [72]. TNFR1 is expressed in all human tissues, while TNFR2 is predominantly expressed in immune and endothelial cells, as well as neurons [73]. Both transmembrane and soluble TNF activate TNFR1, leading to proteolysis of the extracellular domain of TNFR1, which is then released into the bloodstream as sTNFR1 [72, 74]. The production and activity of TNF-α are regulated through the control of TNF gene expression and the release of TNF and its receptors in response to various agonists [75]. It has been suggested that soluble cytokine receptors may better reflect cytokine activity, as they have a longer half-life, are more stable in measurements, and can be detected in plasma even when cytokine levels are undetectable [76, 77]. Thus, sTNFR1 may serve as a marker

of systemic inflammation intensity [78, 79]. Peripheral concentrations of sTNFR1 and sTNFR2 have been studied in various mental disorders, but the role of sTNFR1 in the development of MDD remains unclear. Neuronal TNFR1 is thought to contribute to neuroinflammation and demyelination, as well as axonal damage, oligodendrocyte loss, and the induction of glial cell autophagy through the enhancement of oxidative stress in neurons [80].

Increased concentrations of IgG targeting oxidized LDL in MDD indicate autoimmune responses associated with systemic inflammation — a known mechanism in the pathogenesis of depression [33]. These autoimmune IgG responses in MDD patients are linked to dysregulated lipid-targeting antioxidant defense and repair mechanisms [34]. This is driven by oxidative stress and chronic inflammation [34]. This relationship is particularly noteworthy, because concentrations of IgG to oxidized LDL are directly associated with a coronary artery disorder, which often co-occurs with both MDD and BD [33, 81].

Prospects for future research

Further research into immune system and systemic inflammation markers for distinguishing between MDD and BD offers promising directions for the scientific community. These directions may include:

- The transition from studying individual immune and inflammatory markers to a comprehensive immunoprofiling to determine complex changes in concentrations of cytokines (including chemokines), immunoglobulins, lymphocyte, subpopulations, and other markers in peripheral blood or other biological media. Immunoprofiling provides a broad view of the immune response and can help identify the specific immune profiles associated with MDD and BD.
- For a better understanding of the dynamics of immune and inflammatory markers and their associations with the pathogenesis, progression, and prognosis of MDD and BD, prospective studies are needed. Such studies will allow one to track changes in the immune status depending on the disorder phase and therapy effectiveness.
- Studying disorders beyond the unipolar-bipolar dichotomy: Considering that numerous immune and inflammatory markers are similarly elevated in depressive episodes in both MDD and BD, future research should focus on specific clinical features, such as early onset, high recurrence of affective episodes, subthreshold hypomanic and mixed symptoms, family history, and treatment response.
- Understanding the role of inflammatory and immune markers in the pathogenesis of MDD and BD is essential for developing novel therapeutic strategies aimed at modulating the immune system. For example, drugs targeting specific chemokines or their receptors could represent a promising direction in mood disorder treatment.
- The progress in understanding the role of the immune system in mood disorders requires close interdisciplinary cooperation among psychiatrists, immunologists, and neurobiologists. Such collaboration is crucial for integrating data from diverse fields to create a comprehensive view of the pathogenesis of MDD and BD.

CONCLUSION

The results of this scoping review highlight the complexity and multifaceted nature of the relationship between the immune system and mood disorders. The data suggest potential differences in immune system and systemic inflammation markers in patients experiencing a depressive episode in MDD and BD, particularly in chemokines, PDGF-B, IL-9, sTNFR1, and IgG to oxidized LDL. Studying the role of these markers in the development of mood disorders may be crucial for understanding their pathophysiology and developing more targeted therapeutic strategies. Conversely, immune and inflammatory markers such as IL-1β, IL-4, IL-6, TNF-α, and CRP showed no significant differences between patients with MDD and BD. However, only a limited number of studies considered variables such as the subtype of BD and patient sex, which could impact the interpretation of findings. Further research is warranted to explore the associations between immune system parameters and mood disorders.

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REVIEW

The Mental Health of Refugees and Forcibly Displaced People: A Narrative Review

Психическое здоровье беженцев и насильно перемещенных лиц: нарративный обзор литературы

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Review

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ABSTRACT

BACKGROUND: One of the pressing global issues today is the matter of refugees and forcibly displaced people migration. Refugee or forcibly displaced status has a significant impact on a person's mental health, with a high risk of developing depression, anxiety, post-traumatic stress disorder and psychotic disorders.

AIM: To conduct a literature review and evaluate the mental health status of refugees and forcibly displaced people due to military action

METHODS: The search of literature was conducted without any restrictions on the publication date, with a focus on articles from the past two decades. The search was conducted in the Google Scholar and PubMed databases using the following keywords and phrases: “migration”, “migrants”, “refugees”, “forcibly displaced people”, “mental health”, “mental disorder”, “psychiatric disorders”. This analysis included studies that discussed and evaluated the social, psychological, and clinical aspects of migration. The review included original research and meta-analyses published in English, Russian, and Spanish. Descriptive analysis was applied to summarize the results.

RESULTS: The literature review showed that global migration levels have reached a high point, and this trend continues due to the existing geopolitical conditions. Even limited and difficult-to-compare epidemiological data demonstrate that more than a quarter of migrants suffer from mental disorders. These primarily include depression, anxiety, and post-traumatic stress disorders. Apart from creating and exacerbating problems for the refugees and forcibly displaced people themselves, they also pose serious challenges to the social services and healthcare systems of refugee-hosting countries. The literature review demonstrated that forced displacement plays a role in the development of mental disorders, and also emphasizes the significance of several associated factors.

CONCLUSION: This review emphasizes the urgent need for standardizing screening methods for refugees and forcibly displaced people, creating unified approaches to diagnostic evaluation, as well as specialized training for mental health professionals. Large-scale programs are needed to support and implement sustainable global mental health measures in the countries affected by hostilities.

АННОТАЦИЯ

ВВЕДЕНИЕ: Одной из глобальных проблем современности является вопрос миграции беженцев и насильно перемещенных лиц. Статус беженца или насильно перемещенного лица оказывает значительное влияние на психическое здоровье человека, что сопровождается высоким риском развития депрессий, тревоги, посттравматических стрессовых и психотических расстройств.

ЦЕЛЬ: Провести обзор имеющейся литературы и изучить состояние психического здоровья беженцев и насильно перемещенных лиц в результате боевых действий.

МЕТОДЫ: Проведен поиск литературы без ограничения по дате публикации с акцентом на работы последних двух десятилетий. Поиск осуществлялся в базе данных Google Scholar и PubMed, по ключевым словам и словосочетаниям «миграция» (migration), «мигранты» (migrants), «беженцы» (refugees), «насильно перемещенные лица» (forcibly displaced persons), «психическое здоровье» (mental health), «психическое расстройство» (mental disorder), «психиатрические расстройства» (psychiatric disorders). Исследования включались в анализ, если в них обсуждались и оценивались социальные, психологические и клинические аспекты миграции. В обзор включались оригинальные исследования и мета-аналитические обзорные статьи на английском, русском и испанском языках. Для обобщения результатов применялся метод описательного анализа.

РЕЗУЛЬТАТЫ: Обзор литературы показал, что уровень миграции по всему миру достиг высокой планки, и тенденция к росту сохраняется из-за сложившихся геополитических условий. Даже фрагментарные и трудно сопоставимые эпидемиологические данные показывают, что более четверти мигрантов имеют психические расстройства. Прежде всего, это депрессивные, тревожные и посттравматические стрессовые расстройства. Они создают и усугубляют проблемы не только у самих беженцев и насильно перемещенных лиц, но ставят серьезные задачи перед социальными службами и системой здравоохранения принимающих сторон. Анализ литературы демонстрирует, что вынужденное переселение является патогенетическим фактором в развитии психической патологии, а также подчеркивает значимость ряда сопутствующих факторов.

ЗАКЛЮЧЕНИЕ: Настоящий обзор подчеркивает насущную необходимость унификации методов обследования беженцев и насильно перемещенных лиц, создания единых подходов к обследованию и специальной подготовке специалистов сферы психического здоровья. Необходимы масштабные программы для поддержки и внедрения устойчивых глобальных мер в области психического здоровья в странах, пострадавших от военных действий.

Keywords: *refugees; forcibly displaced people; migrants; social and psychological issues; mental disorders*
Ключевые слова: *беженцы; насильно перемещенные лица; мигранты; социально-психологические проблемы; психические расстройства*

INTRODUCTION

Migration of refugees and forced displacement are among the most pressing issues faced by the international community at the beginning of this third millennium. In light of the destructive trends in the modern world, including political instability, economic crises, numerous local wars and hostilities, climate change, and natural disasters, the issue of migration is moving increasingly to the foreground. The history of humankind is marked by tragic events involving refugees. They emerged on the tail of small and large-scale wars, epidemics, and invasions by nomadic and barbarian tribes. The First and Second World Wars alone led to the displacement of vast numbers of people. Ongoing military conflicts and climatic cataclysms continue to drive mass migration, subjecting people to profound trauma and stress as they relocate to host countries.

Mass population movements in the post-Soviet space began as a result of the collapse of the Soviet Union in 1991, which was characterized by complex interconnections between migration and forced displacement. Interethnic conflicts and national liberation movements in Central

Asia and the South Caucasus in the first half of the 1990s triggered massive flows of refugees and displaced people (in Sumgait, Baku, Nagorno-Karabakh, Abkhazia, South Ossetia, Chechnya, Tajikistan, and Transnistria) [1]. As a result of these processes, a new category of refugees emerged, called forcibly displaced people (FDPs). This category of people was particularly evident when the mass, forced displacement of Armenians from Nagorno-Karabakh, following a prolonged blockade and military aggression by Azerbaijan, put significant pressure on the country's mental health infrastructure which was tasked with providing specialized care for displaced people in need and assessing their mental health status. However, the very phenomenon of such mass displacement highlighted the need to study the psychological and psychiatric impact of migration on a more global scale.

There are two aspects in studying the phenomenon of migration. The first aspect is migration as a distinct process (studied by sociology, history, economics, demography, etc.). The second aspect is migration as one of the factors affecting people's physical and mental health, which falls within the competence of social and health care services, including psychology and psychiatry.

There is still no consensus on the definition of "migration". Russian researchers, for example, have proposed over 30 definitions of this concept. While retaining the generally accepted meaning of this phenomenon, each author offers their own interpretation of the concept of "migration". Some researchers broaden the concept, while others narrow it.

Perevedentsev defines the migration of large numbers of people in a broad sense as "a set of various movements of citizens across space" [2]. In a narrower sense, he views the phenomenon as "a set of relocations of citizens within a territory directly associated with a change of permanent residence for a relatively long period". Barikhin defines migration in a similarly narrow sense: "the movement of people primarily associated with a change of residence and workplace" [3].

Vorobyova offers a rather broad interpretation of migration. She defines the phenomenon as "any territorial movement of populations involving the crossing of both the external and internal borders of administrative-territorial entities with the purpose of changing permanent residence or temporary stay in a territory for study or employment, regardless of whether it occurs under the predominant influence of push or pull factors" [4].

Trifonov defines migration as "a complex process characterized by its uniqueness and dependence on various determinants (social, political, economic, cultural, ideological, and others) and associated with voluntary or forced movement, regardless of whether internal or external administrative-territorial borders are crossed, the length of stay, or the means of transportation used, and carried out for various purposes" [5].

Slobodchikova et al. define migration as "a socio-economic process in which the subject of migration moves with a specific purpose across the borders of territorial entities, regardless of duration and regularity, driven by the interplay of various conditions and factors, typically religious, economic, political, social, or military in nature" [6].

The definition offered by Yudina is the most accurate. She believes that "Migration is the process of population movement across domestic administrative-territorial borders and state borders, driven by changes in residence, employment, education, citizenship, or other reasons" [7].

The International Organization for Migration provides the following definition: "Migration is the process of moving across an international border or within a state. Migration encompasses any kind of movement, regardless of its duration, reasons, or composition"[1]. Pokhlebaeva defines international migration as the movement of individuals, regardless of its form, motives, or duration, from the territory of one state to another, resulting in a change in their legal status, with its regulation, from the moment these individuals cross the border, being governed by the legislation of the hosting state, as well as by international legal documents developed by international organizations focused on addressing migration issues [8].

Understanding the essence of this phenomenon, the complexity involved in defining it, and its multifaceted nature can be made easy by classifying all types of migration. Pokhlebaeva suggests relying on the following criteria: legal (lawful and unlawful), territorial (international and internal), motivational (voluntary [labor: economic, family reunification, professional] and forced [refugees and displaced persons]), duration (permanent and seasonal), and purpose (seeking asylum, obtaining refugee status,

[1] Promotion and protection of human rights, including ways and means of promoting the human rights of migrants: report of the UN General Secretary August 9, 2013. Available from: https://documents.un.org/doc/undoc/gen/n13/422/65/pdf/n1342265.pdf

family reunification, "brain drain", educational, and labor migration) [8].

In the context of this study, international and forced migration are of particular relevance. The first is defined by the act of crossing a state border and the regulation of movement across the border and subsequent stay in the country under the legislation of the host country and international legal norms. Forced migration is caused by various stress factors: civil wars, interethnic conflicts, persecution based on political or ethnic grounds, the threat of physical annihilation, natural disasters, etc. Forced migrants include such categories as refugees and displaced persons [8]. Displaced people are typically classified into two categories: internally displaced and externally displaced. The first category includes individuals who have been displaced within their own country as a result of emergencies or armed conflicts; they are sometimes referred to as internal refugees. The second category includes individuals who have been expelled from their country of citizenship for specific reasons — these are *de facto* refugees [9].

The United Nations defines a refugee as a person who owing to well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of their nationality and is unable or, owing to such fear, is unwilling to avail themselves of the protection of that country.[2]

According to Article 1 of the 1951 Convention, a refugee is a person who, "owing to well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of his nationality and is unable or, owing to such fear, is unwilling to avail himself of the protection of that country; or who, not having a nationality and being outside the country of his former habitual residence as a result of such events, is unable or, owing to such fear, is unwilling to return to it"[3].

As a result of modern geopolitical trends, the issue is becoming increasingly pressing, creating serious social, humanitarian, health, and other challenges. A person leaves their permanent place of residence when their personal safety is threatened and flees to a place where they expect conditions to be better [10]. However, for many displaced people, displacement simply means moving from one impoverished and vulnerable situation to other similarly taxing circumstances.

Forcibly displaced people flee to escape violence. Such a population group is at particularly high risk of mental health challenges [11–13]. The mental health of refugees is challenging for modern psychiatry [14], and as noted at the 25th European Congress of Psychiatry, this challenge will contribute to an increased demand for mental health care among those fleeing wars and persecution [15].

In the study by León-Giraldo et al. [16], conducted in Colombia (one of the countries with the highest number of internally displaced people due to armed conflicts), populations from areas experiencing active armed conflicts were deemed the most vulnerable to mental disorders, particularly individuals aged 18–44 years, women, urban residents, and people with a preschool or primary education. Such populations are only exposed to threats and aggression that violate their fundamental rights; they often face stigma because of their location, which acts as an additional stress factor, further exacerbating their mental health state [17]. Kuwert et al. [18], when evaluating the displacement factor of refugees in conflict zones (in Europe), note that the very act of forced displacement significantly contributes to a decreased overall quality of life and the potential onset of anxiety and depressive disorders. This is also exacerbated by the forced separation from "primary support networks", such as friends and family [19]. Furthermore, these individuals generally have limited access to medical services. All of these limitations hinder recovery from trauma and create a vicious cycle that further violates their rights and impairs their physical and mental health [19]. The displacement of large populations creates significant social and economic challenges and disruptions for host communities. However, a positive contribution of refugees in the long term can also never be excluded [20].

Every day, nearly 34,000 people become forcibly displaced due to wars, conflicts, and natural disasters [21]. More

[2] Statute of the Office of the United Nations High Commissioner for Refugees: Adopted by General Assembly Resolution 428 (V) of 14 December 1950. Available from: https://www.unhcr.org/publications/statute-office-united-nations-high-commissioner-refugees

[3] Convention relating to the Status of Refugees: adopted on 28 July 1951 by the Conference of Plenipotentiaries on the Status of Refugees and Stateless Persons, convened in accordance with General Assembly Statute of the Office of the United Nations High Commissioner for Refugees: Adopted by General Assembly Resolution 429 (V) of 14 December 1950. Available from: https://www.ohchr.org/en/instruments-mechanisms/instruments/convention-relating-status-refugees

than half of them are younger than 18 years of age [21]. According to the World Health Organization (WHO), in 2022, one in eight people globally were displaced.[4] This amounts to nearly one billion people. Of these, 281 million are international migrants and 84 million are FDPs.[4] Among FDPs, there are 35 million children and 1 million children born during the period when their parents were refugees.[4] Factors driving migration (such as poverty, insecurity, lack of access to basic services, armed conflicts, environmental issues, and natural disasters) persist and are even intensifying, suggesting a further increase in the number of displaced individuals.

The status of a refugee or a forcibly displaced people significantly impacts the person's mental health, leading to a high risk of mental disorders such as depression, anxiety, post-traumatic stress disorder (PTSD), and psychotic disorders [22, 23]. And these disorders are more common among refugees, both adults and children, than in the general population [24].

The study aimed to conduct a comprehensive review of the existing literature and to evaluate the mental health implications for refugees and forcibly displaced people as a consequence of hostilities.

METHODS

Eligibility criteria

To study the mental health of refugees and FDPs, we conducted a literature search without any publication date restrictions, focusing on articles from the first quarter of the 21st century.

Information sources

The search was conducted in the Google Scholar and PubMed databases.

Search strategy

The search included various combinations of terms: "refugees", "forcibly displaced persons", "migrants", "mental health", "mental disorder", "psychiatric disorders".

Selection process

Studies were included into the analysis if they discussed and evaluated the social, psychological, and clinical aspects of migration. This review included original research and meta-analyses published in English, Russian, and Spanish, that addressed the mental health issues of refugees. In addition, several articles published before 2000, along with certain official documents from the World Health Organization and the United Nation, and a number of legal and sociological studies were analyzed and referenced for a better understanding the phenomenon of migration.

Data analysys

A descriptive analysis was applied to summarize the results.

RESULTS

When investigating the phenomenon of migration, we identified several key aspects highlighted by the literature review. We analyzed the risk factors for migration, the clinical features of mental disorders in migrants, and the socio-psychological consequences of migration. The results for each aspect are presented below.

Risk factors

Armed conflicts have the most negative impact on people's mental health, regardless of whether individuals are victims of conflicts and military action, members of illegal armed groups, military personnel, or civilians [25]. Such conflicts contribute to mental health disorders in civilians, primarily due to the experience of traumatic events and the fear of their recurrence [17, 26–28], which in turn drive them to migrate. The mental health issues of migrants are numerous, diverse, and complex: the traumatic experiences of displaced people can lead to PTSD, anxiety, depression and somatoform disorders, chronic pain sensations, suicidal tendencies, sleep disruption, and a variety of mental disorders with somatic manifestations (weakness, issues with the cardiovascular, respiratory, gastrointestinal, endocrine, and other systems) [29–32]. The prevalence of mental disorders among displaced people is higher than in the population of the country or region to which they migrate [33], and their health profile differs significantly from that of the host country population [32].

The development of mental disorders can be caused by pre-, intra-, and post-migration events. Silove et al. [34] report that post-migration stress can exacerbate the effects of previous trauma, creating an additional risk to mental health. In particular, it is noted that the prevalence

[4] Refugee and migrant health. World Health Organization; 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/refugee-and-migrant-health

of PTSD is approximately ten times higher among refugees and FDPs than it is among the general population in the host country overall [35].

Refugees and FDPs are more likely to develop depression (e.g., as a reaction to loss), anxiety disorders (as a reaction to uncertainty), and, especially, PTSD (as a reaction to violence and/or torture) compared to the population of the host country [24].

This comes with a high risk of somatic-like responses and existential dilemmas (when beliefs are challenged) [36, 37]. Differences between the migrant's culture and the immigration circumstances (language proficiency, cultural beliefs, disease-related behavior) affect the presentation of mental disorders [38].

For migrants, there are two periods of utmost risk: shortly after migration and after a longer stay in the host country. Some meta-analyses highlight factors that contribute to the prevalence of mental disorders [39]. In particular, the factor of motivation behind a refugee or a FDP phenomenon is discussed. For example, individuals who become refugees for purely economic reasons show twice as low a rate of mental disorders compared to those who migrated due to violence in their country of origin (21% vs 40%) [29].

Many researchers indicate two stable and significant risk factors for the development of mental disorders: past traumatic experiences, and socio-economic conditions after migration [16, 39, 40]. Close et al. consider the low gross national product in the host country, downward social mobility, the country of origin, and the host country as risk factors of mental disorders [41]. The authors believe that the impact of combat-related trauma itself on the current state of mental health is predominant and more significant than post-migration factors.

However, it is also clear that adverse socio-economic post-migration factors also play a role, including unemployment, financial stress, limited language proficiency in the host country, and lack of social support, which more often contribute to the development of depression [42]. However, this data concerning the incidence and prevalence of mental disorders among migrants is contradictory: the role of adverse socioeconomic factors in the development of mental disorders among refugees and FDPs is assessed differently [38]. The WHO report "Mental health of refugees and migrants: risk and protective factors and access to care" specifies that poor socioeconomic conditions following migration can be a contributing factor to the development of mental disorders. Furthermore, the report also suggests that migration can be beneficial to the mental health and well-being of some refugees and migrant groups. It is argued that adverse socioeconomic conditions can exacerbate a pre-existing mental disorder.[5]

Beiser and Hou suggest that persistent and long-term socioeconomic problem can be a predictor of depression even a decade after resettlement [43]. However, according to a longitudinal study by Westermeyer [44] conducted among refugees over a 10-year resettlement period, the level of depression, on the contrary, significantly improved over that period.

The socio-political aspect of life is another adverse factor affecting the mental health of refugees and FDPs according to the literature. This conclusion is based on a large-scale meta-analysis conducted by Porter and Haslam [45]. The authors sought to explore potential factors influencing the mental health status of refugees (internally displaced persons, asylum seekers, and stateless persons), including enduring contextual variables (post-resettlement residence and economic opportunities) and refugee characteristics. They conducted 59 independent comparisons that included 67,294 participants (22,221 refugees and 45,073 nonrefugees). The study demonstrated that refugees had moderately worse outcomes. Post-displacement conditions were found to moderate mental health outcomes. The worse outcomes were observed amongst refugees: 1) living in institutional accommodation, experiencing restricted economic opportunities; 2) displaced internally within their own country; 3) repatriated to a country they had previously fled; or 4) with unresolved conflict in their own country.

Older refugees with higher levels of education, women with higher socio-economic status prior to resettlement and those living in rural areas also performed worse.

The clinical manifestations and dynamics of disorders caused by displacement can be complicated not only by wars and conflicts, which in themselves increase vulnerability to mental disorders, but also by migration and post-migration processes [46]. Such factors include life-threatening displacement, drawn-out asylum procedures,

[5] Mental health of refugees and migrants: risk and protective factors and access to care. Geneva: World Health Organization; 2023. Available from: https://www.who.int/publications/i/item/9789240081840

family separation, unemployment, and discrimination [43, 45, 47–49].

From a clinical perspective, it is extremely important to investigate in greater detail which pre-, intra-, and post-migration factors specifically contribute to the development of symptoms of depression, anxiety, and PTSD [50]. This triad of mental disorders is prevalent among both adult men and women, as well as among pediatric and adolescent refugees and FDPs [51]. However, there are differences in the prevalence rates depending on age [45, 47]. Adolescents and young people have been shown to be more likely to develop PTSD compared to adults [52].

The clinical features of mental disorders in migrants

A person who has left their "past" in their country of residence arrives in a country where they is trying to find their "present" while remaining completely uncertain about the "future". In their "present" life, they faces numerous obstacles, which can be described as "a search for a place in the sun". The multitude of problems make them one of the most vulnerable members of society. The need to go through the circumstances of the move and arrival in a new country, adapt to living conditions in the host country, accept the "rules of the game" in the new community, change established relationships, and accept new life and work conditions. All of this creates new needs and issues that refugees and FDPs have to confront, ranging from household to medical. Their experience of trauma (migration) can increase their susceptibility to various disorders — physical illness, mental, and infectious diseases with varying degrees of severity[6].

The severity of clinical symptoms depends on traumatic life events in their country of origin and is determined by the trauma and deprivation experienced during resettlement. It is also important to consider the role of factors in the host country. Among these are the isolation of migrants, discrimination, wanting social support infrastructure [33], difficulties with social integration and language proficiency, changes in beliefs and worldview, psychological issues, internal diseases, etc. [21, 32, 33]. Refugees and FDPs themselves are a vulnerable group, often exposed to various risk factors related to poverty and lack of access to health and social and social services that could address their health problems. They face a higher risk of developing mental disorders that is the result of the psychological trauma they have experienced. For many of them, diseases occur after migration to the "destination country"[7]. Many of them experience feelings of anxiety and hopelessness, exhaustion, irritability, anger, and they suffer from insomnia and various pain sensations[7].

According to Henkelmann et al. [51], despite the diversity of psychopathological reactions, the majority of refugees and FDPs have a trinity of disorders: anxiety, depression and post-traumatic stress disorder (PTSD). The authors conducted a meta-analysis and systematic review that included 14,882 respondents. They found that the prevalence of diagnosed anxiety and self-report was 13% and 42%, for diagnosed depression and self-report was 30% and 40%, and for diagnosed PTSD and self-report was 29% and 37%. These rates were significantly higher than those observed in the general population, non-refugees, both globally and among populations living in armed conflicts or war zones. These parameters were similar for children, adolescents, as well as adult refugees and were not dependent on the duration of life in a particular region. According to the authors, one in three refugees has diagnosable depression and/or PTSD, and diagnosable anxiety disorders are seen in 1–2 out of 10 refugees. The prevalence of these disorders, based on self-reports, is even higher.

Migrants' health is worse than that of the host population. Close et al. [41] note that first-generation migrants are at a higher risk of mental disorders compared to the local population. Among the most vulnerable individuals are women, especially in matriarchal families; adolescents; elderly people; those who have lost their individual documentation; people with disabilities or with a previously diagnosed mental disorders; victims of violence; and those living in extreme poverty [14]. They often experience xenophobia, discrimination, and stigmatization in the host country, live in substandard housing, are involved in unskilled work and have limited access to medical

[6] Refugee and migrant health. World Health Organization; 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/refugee-and-migrant-health

[7] For the first time, WHO has investigated the health of migrants and dispelled some myths. In Russian. Available from: https://news.un.org/ru/story/2019/01/1347312

care, face difficult life situations, as well as language and cultural barriers[8].

Close et al. [41] provided quantitative data on mental disorders in first generation migrants and the indigenous population based on an analysis of 1,820 reviews. The authors demonstrated that there was a wide variation in prevalence rates in both groups, ranging from 5% to 44%, compared with prevalence rates of 8–12% in the general population.

The prevalence of PTSD was higher among first-generation migrants compared to the local population, ranging from 9% to 36%, compared to a prevalence rate of 1–2% in the general population. The prevalence of anxiety disorders in first-generation migrants demonstrated similar tendencies. The prevalence ranged from 4% to 40% compared with a reported prevalence of 5% in the general population.

The mental health of refugees and FDPs has been extensively researched. Nonetheless, assessing the prevalence of mental disorders among this population has proven to be a challenge dependent on a variety of factors (the country of origin, the country of resettlement, pre-migration traumatic events and experiences, post-migration stress, and post-migration socio-economic status). As noted by Bogic et al. [47], significant discrepancies were observed in the prevalence rates of mental disorders between studies, depending on clinical characteristics and research methodology. For example, the prevalence of depression ranged from 2.3% [43] to 80% [39], PTSD from 4.4% [40] to 86% [39], and anxiety disorders from 20.3% [53] to 88% [39]. Several reviews on this issue also highlight significant discrepancies in the prevalence rates of mental disorders, ranging from 5% to 80% for depression and from 3% to 88% for PTSD [47, 54]. Fazel et al. [52] report a prevalence of 4–6% for depression and 8–10% for PTSD in adult refugees. Lindert et al. [29] and Steel et al. [55] report a significantly higher prevalence of depression (25–45%), anxiety disorders (21–35%), and PTSD (31–63%) among this group of refugees compared to economic migrants.

Mental health disorders may not manifest themselves immediately during the migration process, but days, weeks, months or even years later. Even five or more years after resettlement, high prevalence rates ranging from 20% or higher have been reported in war refugees [16]. Based on a study conducted by Sabin et al. [56], two decades after the conflict, 12% of the people examined showed symptoms that fit the diagnostic criteria for PTSD. More than half of them (54%) had symptoms of anxiety; and more than a third (39%), symptoms of depression. A similar trend was reported by Steel et al. [40]. Another study [57] found that refugees exhibit pronounced somatic symptoms when seeking medical care for their mental health issues. Refugees and FDPs are approximately 14 times more likely to develop depression and 15 times more likely to develop PTSD [58–60].

PTSD is considered a common manifestation of mental disorder among refugees and FDPs. However, this disorder is rarely diagnosed as a standalone condition. It is usually accompanied by psychopathological symptoms. For example, Belz et al. [61], confirming the high prevalence of PTSD among refugees with symptoms of intrusion, hyperarousal, avoidance, and dissociation associated with pre-, intra-, and post-migration events, also reported a high level (94%) of comorbid depression in PTSD patients. This pattern of mental disorders creates additional challenges for mental health professionals and the health care system, as such cases are associated with reduced cognitive abilities, energy levels, motivation, learning capacity, and decision-making ability [62], which further complicates PTSD therapy [63]. In general, these studies showed a clear (40-fold) difference in prevalence rates, indicating a high degree of statistical heterogeneity. Such a high level of heterogeneity was also reported in other systematic reviews and meta-analyses [45, 55].

On the path to social integration, refugees and FDPs face serious hurdles related to employment, xenophobia, racism, mental health, physical safety, accommodation, health care, and quality of life.

Traumatic experiences can also lead to the development of specific phobias, personality disorders, and dissociative disorders [64]. Significant differences in the prevalence of alcohol abuse and psychotic disorders among refugees and internally displaced people were noted by Morina et al. [65]. Suicidal tendencies and thoughts are common among refugees and FDPs [16].The authors attribute their occurrence more to depression than to anxiety,

[8] Convention relating to the Status of Refugees: adopted on 28 July 1951 by the Conference of Plenipotentiaries on the Status of Refugees and Stateless Persons, convened in accordance with General Assembly Resolution 429 (V) of 14 December 1950. Available from: https://www.ohchr.org/en/instruments-mechanisms/instruments/convention-relating-status-refugees

even though anxiety is more pronounced than depression [66]. One of the most common symptoms experienced by refugees and FDPs is sleep deprivation, which can exacerbate other disorders and interfere with the ability to function daily [67, 68].

Researchers pay special attention to people over 60, whose needs are often ignored and who do not have access to special support programmes. This exacerbates the vulnerability of the elderly affected by natural disasters, catastrophes and wars.[9] According to Singh [69] pronounced depressive and anxiety syndromes were noted among temporarily displaced elderly people as part of general distress. The authors also described such psychosocial issues as feelings of abandonment, isolation, and passivity, as well as conflicts in the family.

The analysis of the mental disorders identified in refugees and FDPs reveals a number of gender-specific characteristics. It has been found that the prevalence rates of depression and anxiety are typically higher in women than in men [58, 70, 71]. Researchers have different opinions on PTSD. It has been found that both men and women are equally likely to be at a high risk of PTSD. However, this contradicts previous findings in the general population, which suggest that women are more likely to develop PTSD [72, 73]. However, this finding is consistent with the results of a previous meta-analysis of a population affected by war [55]. In the general population, men and women typically differ in their types of traumatic experiences: the most common PTSD-related traumatic events for men are combat experiences, while for women they are rape and sexual harassment [73, 74]. Both the civilian male population and women can be exposed to similar traumatic events during war [75].

As well as mental health issues, somatic mordibilities are often prevalent during humanitarian crises in low- and middle-income countries. However, the prevalence of these mordibilities is significantly underestimated in the current health services research [76]. As noted by Cheung et al. [76], over half of examined migrants (55%) were identified as being at moderate (18%) or high (13%) risk of somatic distress. The authors also reported that there were significant associations (p <0.05) between somatic distress and age, female sex, economic status, depression and post-traumatic stress, and multiple trauma exposures. It is worth noting that high detectability of internal diseases is a reliable predictor of care-seeking behavior [76].

The socio-psychological consequences of migration

In addition to specific disorders and syndromes, the deterioration of physical and mental well-being, wars, mass forced displacement, and human rights violations can have a profound impact on the worldview of refugees and FDPs. In a study investigating cognitive representations of the world globally, Ter Heide et al. [77] found that refugees exhibited a relatively low level of perceived benevolence of the world and people's kindness, and a relatively good sense of their own self-worth. The authors highlight the need to take into account refugees' attitude towards society, particularly the loss of trust, when communicating with them and assessing their condition. Addressing these issues may help ease the adaptation of vulnerable individuals. Bäärnhielm et al. [21] emphasize the need to promote a positive public image of refugees in host countries, alongside addressing their trauma and mental health needs, to support their well-being and social integration. They also stressed the importance of involving refugees in elaborating policy, planning, development, and the delivery of services that cater to them [78].

Most research on refugees and FDPs is conducted in countries with developed economies that can provide relatively high levels of support and opportunities for integration. However, for the sake of objectivity, it is also worth noting that most of these migrants had lived in low-income countries. Their struggles to survive and make plans for the future make their mental health situation particularly difficult. The granting of asylum should be accompanied by the provision of health care, including mental health support, to help mitigate the negative impact of migration.

DISCUSSION

This literature review included original research and meta-analyses. As a result of recent geopolitical trends, migration is becoming an increasingly critical issue, creating serious humanitarian, social, health, and other challenges. It has become increasingly dangerous and problematic to live in the place of one's birth, as due to various reasons, threats

[9] World Development Indicators/databank. Available from: https://databank.worldbank.org/reports.aspx?source=2&series=sp.pop.65up.to.zs&country=

to personal security arise and a person flees to a place where they expect conditions to be better [10]. Factors contributing to mass displacement (such as poverty, insecurity, lack of access to basic services, armed conflicts, environmental issues, and natural disasters) are increasing and even intensifying, suggesting further increase in the number of displaced people and the growing relevance of this issue in the global community.

The resettlement of large groups of people can occur within their own country (internal displacement) or across national borders into neighboring or other countries (as asylum seekers) [12]. However, we could not find any article on refugees that had looked into a situation similar to the one that occurred in Nagorno-Karabakh. The peculiarity of this resettlement was that the people who were fleeing from violence and aggression in their ethnic territory [79] did not move to a third country. Instead, they resettled in their historic homeland, which they were forced to leave by political decisions. They were settled not in refugee camps (as is the case almost everywhere), but in the apartments and houses of their fellow citizens. On the one hand, this is a flight across national borders to an adjacent country, and on the other hand, it is a resettlement in a country that is their historic homeland with a shared history, culture, language, and religion. This peculiarity, from our point of view, requires special attention.

The fact that people who have been exposed to extreme stressors such as wars, natural disasters, social catastrophes, and others, are resettled, puts the problem of health, including mental health, in the forefront [29, 30]. Regardless of whether these disorders are transient, acute, or situationally determined, they tend to chronicle and inhibit the full development of a person's potential [26, 27].[10]

In addressing mental health issues caused by migration, priority must be given to understanding the processes underlying the phenomenon of migration and the factors contributing to the development of mental disorders. The literature highlights a range of factors, including armed conflicts and social upheaval (or past-traumatic experiences), socio-economic and socio-political conditions, the motivational factors of refugees [29], migration and post-migration processes (life-threatening movements, long asylum procedures, family separation, unemployment, discrimination [39, 80],conditions in the host country, problems with social integration, insufficient social support, worldview and psychological problems, internal diseases, etc. [21, 32, 33]). Factors such as low gross national product in the host country, downward social mobility, the country of origin, and the host country are considered risk factors for mental disorders [16, 39–41]. At the same time, while highlighting numerous risk factors, the impact of the trauma on the current state of mental health is not denied; moreover, its leading significance compared to post-migration factors is emphasized.

There is a lack of consensus on the impact of adverse factors on the emergence of mental health issues among refugees and FDPs. A comprehensive meta-analysis conducted by Porter and Haslam [45] demonstrated that post-displacement conditions had a significant impact on the mental health of refugees and FDPs. These conditions include living in institutional accommodation, experiencing restricted economic opportunities, repatriation to the home country, or unresolved conflict. Undoubtedly, the lack of social support plays a negative role in the development of mental disorders, particularly depression [64]. Certain demographic factors also negatively affect the development of mental disorders. These factors include age >60 years, high education level, and being female.

The nature, intensity, and duration of exposure to risk factors, as well as a specific psycho-emotional background before, during, and after migration, can explain the high prevalence of mental disorders. Many researchers highlight two stable and significant risk factors behind the development of mental disorders: past traumatic experiences and socio-economic conditions after migration (unemployment, financial stress, poor language skills in the host country, and lack of social support) [16, 39, 40, 42].

However, these results regarding the incidence and prevalence of mental disorders among migrants are contradictory [38].

For migrants, there are two periods of elevated risk: shortly after migration and after a longer stay in the host country. Differences between the migrant's culture and the immigration circumstances (language proficiency, culture, disease-related behaviors) affect the character of mental disorders [38]. However, among all the events contributing to the forced displacement of people, military actions play a special role, as they cause widespread mental

[10] Galderisi S. Opening ceremony. Flolence: Programme of the 25th EPA Congress, 2017.

disorders even many years after the end of the war and resettlement.

Health issues among refugees and FDPs have been shown to be diverse, numerous, and complex. The traumatic experiences of displaced people can lead to PTSD, anxiety, depressive, and somatoform disorders, chronic pain sensations, sleep deprivation [67], various mental health issues, suicidal tendencies [16, 66], and somatic symptoms affecting multiple organs and systems (cardiovascular, respiratory, musculoskeletal, gastrointestinal, immune, endocrine, and other systems) [29–31, 76]. There is a high risk of somatised reactions and existential problems (when stereotypical beliefs are challenged) [36, 37] personality and dissociative disorders [64], alcohol abuse and psychotic disorders [65].

Moreover, these mental disorders may be the result of experiences related to pre-, intra-, and post-migration events. It is noted that post-migration stress can exacerbate the effects of prior trauma, creating an additional risk to mental health [34]. In particular, it is noted that the prevalence of PTSD is approximately ten times higher among refugees and asylum-seekers than among the population in the host country [81, 32, 35].

Despite the diversity of psychopathological responses among refugees and FDPs, the most common clinical manifestations are anxiety (13%), depression (30%), and PTSD (29%) [51]. According to self-reports, the prevalence of these disorders is much higher: anxiety was reported by 42%, depression by 40%, and PTSD by 37% of refugees and FDPs. Moreover, the indicators did not depend on the duration of residence in a particular neighbourhood according to Henkelmann et al. [51].

Data from various authors on the prevalence rates of anxiety, depression, and PTSD among refugees and FDPs show a significant variation, which complicates an accurate, reality-based assessment of the prevalence of these disorders [29, 39, 43, 47, 52–55]. This also indicates a high degree of statistical heterogeneity [45, 55, 64].

The integration process of refugees and FDPs is complicated by serious challenges related to employment, xenophobia, racism, physical safety, accommodation, and overall quality of life. All these problems are accompanied by mental pathology, unless they are followed by psychological phenomena: anxiety, fear, emotional tension, anger, powerlessness, hopelessness, worthlessness of one's own existence, passivity and despair suicidal thoughts [68].

The lack of special programmes for persons over 60 years of age exacerbates the vulnerability of older persons [70] in displacement following natural disasters, catastrophes and war[11]. This social group has been found to display significant symptoms of distress in the context of depressive and anxiety syndromes, as well as psychosocial problems such as feelings of abandonment, isolation and passivity, and suffering from intra-family conflicts [69].

Women are a particularly vulnerable group among refugees and FDPs, as they are more prone to depression and anxiety [60, 72, 73]. In relation to PTSD, differences between the sexes have been noted in the types of traumatic experiences: in women, it is rape and sexual harassment [74–76].

In addition to psychosocial and mental problems during humanitarian crises in low- and middle-income countries, a high prevalence of internal diseases is also observed [77]. However, significant correlations are noted between internal diseases, age, female gender, and mental disorders, a high level of each being a reliable predictor of care-seeking behavior [77].

In addition to specific disorders and syndromes, the deterioration of physical and mental well-being, wars, and mass forced displacement can have a profound impact on the worldview of refugees and FDPs. They exhibit a relatively low level of perceived benevolence of the world and the warmth of people, loss of trust. This should be taken into account in the process of communication, development of rehabilitation programmes, formation of positive public attitudes towards refugees [21, 46, 79].

There is no doubt that the resettlement of large numbers of people and migration policies raise many ethical, political and organisational issues, in addition to health issues. These issues need to be constantly discussed and resolved [78, 82, 83]. The key to effective intervention and its implementation is the involvement of a wide range of local and global actors [84].

Limitations

The primary limitation of this article is its narrative, rather than systematic, review format, which may have resulted in the omission of relevant studies on this topic.

[11] Mental health of refugees and migrants: risk and protective factors and access to care. Geneva: World Health Organization; 2023. Available from: https://www.who.int/publications/i/item/9789240081840

A non-systematic search for information was conducted, and articles of any type that evaluated the social, psychological, and clinical aspects of displacement were included in the study; the quality of the included studies was not assessed. Many of the included studies had a low level of evidence. These limitations may cloud a more complete understanding of the issue. Therefore, the conclusions drawn in this article may be preliminary.

A key strength of the present study is the identification of the role of various factors contributing to the development of mental disorders among refugees and FDPs.

CONCLUSION

The data presented in this review highlight the importance and relevance of the issue of refugees and FDPs for any society, as well as for specific services that aim to realistically assess the problem in each individual case and respond appropriately to the needs of migrants. Available limited and difficult-to-compare epidemiological data demonstrate that more than a quarter of migrants suffer from mental disorders requiring therapy, although access to such treatment is often difficult to achieve.

The data obtained clearly demonstrate that forced displacement plays a role in the development of mental disorders. The importance of other accompanying and contributing factors is emphasized — the role of factors in the host country, such as the isolation of migrants, discrimination, stigmatization, insufficient social support, changes in beliefs and worldview, psychological issues and internal diseases, language and cultural barriers, etc. Medical and social support for refugees and FDPs should be based on a clinical assessment of their mental health, the factors that led to their displacement, the cultural characteristics of the migrants, and the socio-economic and socio-political conditions in their home country. It should also be guided by the principles of humanism and tailored to each individual. In this process, it is crucial to rely on both governmental and community organizations, which should complement each other. To address the problem of mental health and implement social programs, an open dialogue is necessary between displaced people and the host communities at all levels (municipal, state, economic, and political, as well as business entities and public organizations).

This review emphasizes the urgent need to standardize screening methods for refugees and forcibly displaced people and create consolidated approaches to diagnostic evaluation, as well as specialized training for mental health professionals.

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Integrating Rational Emotive Behavior Therapy, Compassion-Focused Therapy with Cognitive Retraining in Traumatic Brain Injury: A Case Report

Интеграция рационально-эмоционально-поведенческой терапии и терапии, сфокусированной на сострадании, с когнитивной реабилитацией при травматическом повреждении головного мозга: клинический случай

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Case report

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ABSTRACT

BACKGROUND: This case report presents a novel approach to treating Traumatic Brain Injury (TBI) by integrating Rational Emotive Behavior Therapy (REBT), Compassion-Focused Therapy (CFT), and Cognitive Retraining (CR). It contributes to the literature by demonstrating the effectiveness of a comprehensive psychotherapeutic approach in managing complex TBI sequelae, particularly in the Indian context where such interventions are underrepresented.

CASE REPORT: A 34-year-old Indian female presented signs of emotional dysfunction, cognitive impairment, social maladaptation, shamefulness, and self-deprecation following a TBI sustained 10 years prior. A mental status examination and psychological assessments revealed cognitive deficits, emotional instability, and irrational beliefs, all related to her injury and recovery. The treatment plan integrated REBT, to address the irrational beliefs; CFT, to manage the sense of shame and the insistence to self-criticize; and CR, to improve cognitive functions. This approach was tailored to the patient's cognitive limitations and cultural context. Interventions included challenging irrational beliefs, self-compassion imagery, and cognitive exercises adapted to her specific deficits. Outcomes were measured using the Subjective Units of Distress (SUD) scale and clinical observations. The patient showed improvements in emotional regulation, cognitive functioning, and overall quality of life, as evidenced by reduced subjective distress (SUD down from 90 to 58) and enhanced daily functioning.

CONCLUSION: This case demonstrates that an integrated psychotherapeutic approach combining REBT, CFT, and CR can effectively address the complex psychological and cognitive challenges of TBI patients. Tailoring interventions towards patient cognitive limitations and cultural context is crucial for a successful outcome. The case highlights the importance of incorporating diverse therapeutic modalities in TBI management, promoting a more holistic approach to recovery and enhancing the quality of life of TBI survivors.

АННОТАЦИЯ

ВВЕДЕНИЕ: В данном клиническом случае представлен новый подход к лечению черепно-мозговой травмы (ЧМТ) путем интеграции рационально-эмоционально-поведенческой терапии (rational emotive behavior therapy, REBT), терапии, ориентированной на сострадание (compassion-focused therapy, CFT), и когнитивной реабилитации

(cognitive retraining, CR). Работа вносит вклад в имеющуюся литературу, демонстрируя эффективность комплексного подхода к терапии тяжелых последствий ЧМТ, особенно в Индии, где подобные вмешательства представлены недостаточно.

КЛИНИЧЕСКИЙ СЛУЧАЙ: 34-летняя женщина из Индии (пациентка VR) обратилась с жалобами на нарушения эмоциональной регуляции, когнитивные расстройства, социальные трудности, чувство стыда и самообвинение, возникшими после ЧМТ, перенесенной 10 лет назад. Психиатрическая оценка выявила наличие нарушений когнитивных функций и эмоциональной сферы, а также иррациональных убеждений относительно ее травмы и восстановления. План лечения включал сочетание REBT для коррекции иррациональных убеждений, CFT для облегчения чувства стыда и самообвинения и CR для улучшения когнитивных функций. Данный подход был адаптирован с учетом когнитивных ограничений пациентки и культурного контекста. Вмешательства включали оспаривание иррациональных убеждений, визуализацию образов для развития самосострадания и когнитивные упражнения, направленные на нарушенные у данной пациентки функции. Результаты оценивались с помощью шкалы субъективных единиц дистресса (SUD) и показателей клинических наблюдений. Пациентка продемонстрировала улучшения в эмоциональной сфере, когнитивных функциях и общем качестве жизни, о чем свидетельствовали уменьшение субъективного дистресса (оценка по SUD снизилась с 90 до 58 баллов) и улучшение повседневного функционирования.

ЗАКЛЮЧЕНИЕ: Данный клинический случай демонстрирует, что интегрированный психотерапевтический подход, состоящий из REBT, CFT и CR, может эффективно решать сложные психологические и когнитивные задачи у пациентов с ЧМТ. Адаптация вмешательств с учетом когнитивных ограничений и культурного контекста пациента является важным фактором успешного лечения. Случай подчеркивает важность включения различных терапевтических методов для целостного подхода к восстановлению и улучшению качества жизни пациентов, перенесших ЧМТ.

Keywords: *psychotherapy; traumatic brain injury; cognitive rehabilitation; case report*
Ключевые слова: *психотерапия; черепно-мозговая травма; когнитивная реабилитация; клинический случай*

INTRODUCTION

Traumatic brain injury (TBI) is a major global health concern with far-reaching consequences for individuals, families, and society worldwide [1]. Often referred to as the "silent epidemic", TBI significantly contributes to disability and fatality rates globally [2]. Recent estimates indicate that over 69 million people suffer a TBI each year, with Southeast Asia and the Western Pacific regions bearing the heaviest burden [3].

In developing nations like India, the TBI burden is particularly concerning due to increasing industrialization, motorization, and changing social norms [4]. The impact on individuals and society is significant, yet there is a notable lack of research on TBI prevention, rehabilitation, and management in this context [4]. TBI can manifest itself in various conditions, including cognitive deficit, emotional dysfunction, difficulties to function, and sensory issues[1].

While cognitive rehabilitation has traditionally been emphasized in TBI management, psychotherapeutic approaches have received less recognition. Recent studies have explored various psychotherapeutic modalities [5, 6]. Building on this literature, we present a case study that integrates Cognitive Retraining (CR) with Compassion-Focused Therapy (CFT) and Rational Emotive Behavior Therapy (REBT) as a comprehensive psychotherapeutic management approach for TBI [7].

This case report of a middle-aged female highlights the multifaceted challenges faced by TBI survivors on a global level. By presenting this integrated approach, we aim to address the gap in the literature regarding a comprehensive psychotherapeutic management of TBI, particularly in the Indian context.

Our aim was to investigate the effectiveness of an integrated psychotherapeutic approach combining REBT,

[1] Available from: https://msktc.org/tbi/factsheets/understanding-tbi-part-2-brain-injury-impact-individuals-functioning

CFT, and CR in managing the complex psychological and cognitive sequelae of TBI. Specifically, we sought to do the following:

- address the gap in the existing literature regarding a comprehensive psychotherapeutic management of TBI, particularly in the Indian context [8–10];
- demonstrate the potential benefits of a holistic, patient-centered approach that factors in cognitive limitations, cultural factors, and individual needs;
- explore the synergistic effects of combining multiple evidence-based therapeutic modalities (REBT, CFT, and CR) in improving emotional regulation, cognitive functioning, and overall quality of life for TBI survivors;
- contribute to the growing body of evidence that supports the use of integrative approaches in neurorehabilitation, emphasizing the importance of psychological interventions alongside cognitive rehabilitation;
- highlight the need for tailored, flexible interventions that address both the cognitive and emotional aspects of TBI recovery simultaneously;
- provide insights into the practical application and potential efficacy of this integrated approach, laying the groundwork for future, more rigorous studies in the field of TBI rehabilitation.

CASE REPORT

Patient information

General information

Patient VR, a 34-year-old female from an urban area, complained of a decade-long history of forgetfulness, difficulty walking, and irritability, alongside a persistent low mood lasting around six years. These symptoms appeared following a TBI sustained 10 years earlier, resulting in a 27-day coma and extensive treatment. She experienced significant psychological, emotional, social, and physiological challenges, including emotional instability, depressive symptoms, and cognitive deficit. Ongoing stressors, such as interpersonal and marital issues, exacerbated her difficulties.

Medical, family, and psycho-social history

Magnetic resonance imaging (MRI) tests revealed gliotic areas in the right temporal lobe, bilateral anterior frontal lobe, vermis, and the cerebellar hemispheres, with a diffuse volume loss in the midbrain and brainstem. The patient had a well-adjusted premorbid personality and no significant psychiatric family history. High parental expectations during childhood contributed to her internalized belief in perfectionism, causing distress across the personal, professional, and social domains.

Six months post-accident, the patient was still undergoing treatment from the hospital on an outpatient basis. The patient encountered frequent challenges during travel as her parents were elderly. To mitigate these challenges, online therapy sessions were integrated into her treatment plan to supplement in-person appointments.

The patient, a female in her late thirties, from a middle-class socioeconomic background, is educated, with an upbringing characterized by high parental expectations. The parents instilled in her the need to strive for perfection in all life endeavors. She has encountered several life challenges, including TBI, acculturative stress, job loss, and marital dissolution. These experiences have led her to internalize the belief that she must always meet high standards, fulfill others' expectations, and seek their approval.

These core beliefs in turn act as internal mandates by creating a constant drive to achieve and gain the expected validation. During challenging circumstances, these beliefs activate the internal threat system that makes her perceive such situations as fraught with potential failures or rejection. That in turn triggers in her a sense of shame, fear and self-doubt.

This behavior manifests itself in different ways:

- Drive to be flawless: she engages in behavior aimed at achieving perfection in everything she does.
- Quest for reassurance: she constantly seeks validation from others.
- Inadequate soothing system: her reliance on external validation fails to alleviate distress, reinforcing her core belief that she needs external approval to feel okay.

Her very demanding values system can further elevate the level of perceived threat in challenging situations and her beliefs in the awful likely exacerbate distress and contribute to a negative self-image.

She has unmet core needs for protection, self-worth, and compassion. The psychological consequences of these unmet needs and her core beliefs include depression, low self-esteem, social withdrawal, procrastination, difficulty with daily activities due to cognitive challenges from TBI, and impulsivity.

Her TBI has resulted in cognitive issues such as memory difficulties, executive dysfunction, slowed information processing, and the ability to think in concrete terms. The patient experiences emotional problems such as emotional dysregulation, low mood, low self-esteem, and functional problems such as social withdrawal and difficulties in daily living. She also developed various sensory issues linked to her TBI.

The activation of her threat-management capability fuels her drive, leading to behavior that seeks to achieve perfection and validation. When this behavior fails to alleviate her distress, a sense of disappointment that reinforces her core beliefs takes hold, further straining her soothing system. This cycle results in constant pressure and fear, which manifests itself in depression, low self-esteem, and social withdrawal. The cycle of distress she is trapped in is presented on Figure 1.

Clinical findings

Upon a detailed assessment and examination, the patient was presented with a constellation of symptoms indicative of the significant neuropsychological implications of her TBI and her MRI findings. They included forgetfulness, decreased interest in pursuing any activities, low mood and slow gait, impaired immediate, recent memory, impaired social and personal judgment with ideas of hopelessness and helplessness. Psychological assessments identified deficits in cognitive domains such as speed of processing information, difficulty in sustaining attention, divided attention, verbal working memory, verbal fluency, verbal learning and memory, visual learning, logical memory, visual recognition, and retention. Additionally, other assessment results highlighted the experience of low mood, depressive tendencies, withdrawal, feelings of inferiority, and regression. Beck's depression inventory [13] was administered as a baseline assessment of subjective complaints wherein the patient presented complaints such as low mood, decreased interest in undertaking any work, and irritability. Further, interpersonal issues, which included marital adjustment problems exacerbated by the expressed emotions of her mother, resulted in emotional distress. Despite all these challenges, VR showed resilience

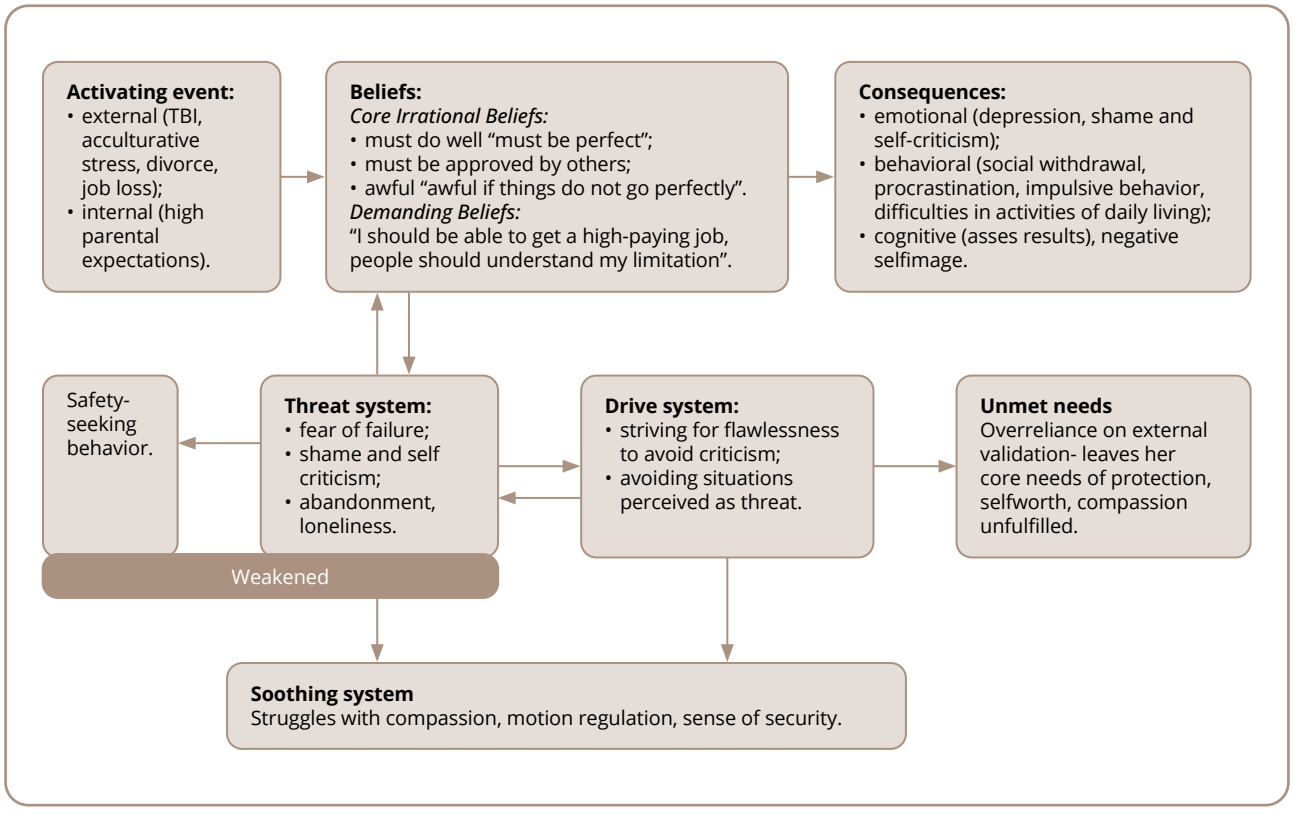

Figure 1. Psychotherapeutic formulation using REBT&CFT models, modified and compiled together by the authors [11, 12].

Note: TBI — Traumatic Brain Injury; REBT — Rational Emotive Behavior Therapy; CFT — Compassion-Focused Therapy.

Source: Mahajan et al., 2024.

and determination from the patient, who continued to actively participate in treatment.

Furthermore, her symptoms hinted at a possible organic condition or cognitive impairment, as indicated by regression and a withdrawn emotional state, which aligned with the ICD-10 diagnosis of F06.32 Organic mood (affective) disorder [14]. Thus, considering all these factors, psychotherapeutic intervention was deemed necessary.

Diagnostic assessment

Diagnostic testing

The diagnostic assessment included a comprehensive battery of tests and examinations. The MRI findings revealed gliotic areas in multiple brain regions, indicating widespread damage consistent with diffuse axonal injury. A psychological assessment, including the Depression Anxiety and Stress Scale (DASS), Human Figure Drawing Test (HFDT), National Institute of Mental Health and Neurosciences (NIMHANS) Neuropsychological Battery, and Beck Depression Inventory (BDI), was conducted. The DASS results contained a score of 28 for depression (interpreted as extremely severe), 8 for anxiety (mild), and 18 for stress (mild). The HFDT, which also serves to build rapport, presented a complex array of psychological symptoms including anxiety, depressive tendencies, withdrawal, feelings of inferiority, regression, and low energy levels. That suggested high aspirations hindered by diminished energy, fixation on past events, feelings of futility, and lack of achievement, indicating a significant emotional burden and hinting at possible organic conditions or cognitive impairment. The NIMHANS Neuropsychological Battery identified deficits in processing speed, sustained and divided attention, verbal fluency, verbal learning and memory, set shifting, verbal working memory, visual learning, and logical memory, in alignment with the diffuse nature of the brain injury.

Diagnostic challenges

The diagnostic process for VR presented several significant challenges. Foremost was the difficulty in differentiating between organic causes stemming from the TBI and psychological reactions to trauma, as symptoms could be attributed to both. This interplay made it challenging to distinguish cognitive deficits directly resulting from brain injury from those potentially exacerbated by emotional distress. VR's cognitive impairments necessitated adaptation to standard assessment procedures, potentially leading to an underestimation of her abilities due to deficits in processing speed and attention. Cultural and contextual factors added another layer of complexity, requiring careful consideration of how cultural beliefs and societal expectations might influence symptom presentation and interpretation. Finally, the long-term nature of VR's condition, with symptoms persisting and evolving over a 10-year period since the initial injury, presented challenges in accurately assessing the progression and changes in the patient's clinical picture over time.

Diagnosis

Primary diagnosis: F06.3 Organic mood (affective) disorder (ICD-10) [15].

Other considered diagnosis: F07.2 Postconcussional syndrome (ICD-10).

Prognosis

The prognosis picture for VR is mixed, with both positive and challenging factors to consider. On the positive side, VR has shown responsiveness to the integrated psychotherapeutic interventions, evidenced by a reduction in subjective distress levels (Subjective Units of Distress, SUD [16], down from 90 to 58) and reports of enhanced ability to function. SUD is a self-assessment tool used to measure the intensity of distress or anxiety on a scale from 0 to 10, where 0 represents no distress and 10 represents the highest level of distress imaginable [16]. The patient's active involvement in treatment and the support from family members are also favorable prognostic indicators. However, several factors warrant a more guarded outlook. The chronic nature of the TBI, with symptoms persisting for over a decade, suggests that some of the deficits may have become permanent. The severity of her depression (shown as extremely severe on the DASS) and the presence of occasional self-harm ideation indicate ongoing mental health vulnerabilities. Cognitive deficits across multiple domains, as revealed by the NIMHANS Neuropsychological Battery, may limit the chances of the patient to fully recover her ability to function. Additionally, the risk of developing secondary complications or mental health issues remains a concern. Environmental stressors and the challenge of sticking to the treatment plans in the long term could also impact her recovery trajectory. Given these factors, the long-term prognosis is cautiously optimistic, but with the expectation of ongoing challenges.

Therapeutic intervention

Relevant interventions with outcomes

Patient VR is currently undergoing psychotherapeutic treatment with pharmacotherapy, including escitalopram, risperidone, and venlafaxine. To gain insight into patient strengths, weaknesses, and emotional state, various relevant psychological assessments were administered with adaptation of the process of administration to her difficulties. The assessments included DASS [17], HFDT [18], the NIMHANS Neuropsychological Battery [19], and two subtests of the Post graduate institute battery of brain dysfunction [20].

The psychotherapeutic management approach took into account the cultural and religious aspects and incorporated a combination of REBT, CFT, and CR spread across the sessions. The sessions involved rapport establishment, psychoeducation, addressing and exploring the emotional impact and cultural beliefs, and curating techniques tailored to her cognitive limitations, as well as keeping the sessions short between 35 and 40 mins.

Types of therapeutic intervention

The following therapeutic interventions were used on the patient (Tables 1 and 2).

1. CR.
2. REBT.
3. CFT for the family:

- training family members on active listening skills;
- teaching assertive communication techniques (e.g., using 'I' statements, expressing needs clearly);

Table 1. The techniques and intervention procedures used during psychotherapy sessions originally by the authors

Session	Techniques	Procedure
1	Rapport building, explaining therapy process	Established a trusting and collaborative relationship. Explained the therapy process, including duration, typical flow of sessions, and ethical considerations (confidentiality, etc.).
2	Explore self-harm ideation	Explored any history of self-harming thoughts or attempts. Discussed about occasional thoughts of self-harm.
	Address the emotional impact of TBI and cultural beliefs	Explored feelings of guilt, helplessness, self-criticism, and shame related to cultural beliefs and TBI.
3	Address sexual health concerns	Assessed comfort level and specific questions about sexuality and reproduction. Provided psychoeducation about sexual intimacy, intercourse, conception, and childbirth. Debunked myths surrounding these topics using basic diagrams and analogies.
	Educated caregivers	Conducted separate sessions with caregivers to facilitate open communication and expression of emotions. Provided information about TBI, its psychological effects, and supportive strategies for recovery.
4	Promoted self-awareness and self-management	Introduced weekly schedule planning to manage activities. Practiced a short body scan relaxation technique.
5	Introduced CBT	Discussed CBT as a potential therapeutic approach after initial discussions and goal setting. Explained the concept of CBT case formulation and its potential benefits in patient treatment.
6	Adapted therapy approach to cognitive limitations	Acknowledged patient difficulty in understanding CBT due to the impact of brain injuries on ability to process information and undertake cognitive tasks. Emphasized that different people have different therapeutic needs and that finding a suitable approach is crucial. In a supportive manner and with empathy, inquired about the specific challenges she faced with CBT. Explored alternative therapeutic options that would align with patient learning style, cognitive abilities, and goals were refined.
7–9	Manage emotional distress	Implemented a multifaceted approach combining: • REBT to identify and challenge harmful beliefs contributing to her emotional distress; • CFT to cultivate self-compassion and manage stress using techniques like soothing rhythm breathing and calming body scans (adapted for patient cognitive limitations); • CR to improve cognitive functioning.
10–12	CFT techniques	Introduced CFT techniques like soothing rhythm breathing and calming body scans, adapted for her cognitive limitations, to help patient manage stress and cultivate self-compassion.
13–14	Conducted a neuropsychological assessment	Administered a comprehensive neuropsychological assessment to evaluate her cognitive functioning in more detail.
15–16	Reinforced previously learned concepts	Reviewed and re-addressed concepts previously discussed in therapy. Social skills exploration activity.

Note: TBI — Traumatic Brain Injury; CBT — Cognitive Behavioral Therapy; REBT — Rational Emotive Behavior Therapy; CFT — Compassion-Focused Therapy; CR — Cognitive Retraining.

Table 2. Cognitive domains with deficit, related exercises with description created and used during therapy sessions

	Exercises	Description
Processing speed	Cooking, cleaning	Engaging in household tasks that require quick decision-making and coordination.
	Sudoku, crossword puzzles	Solving puzzles that require fast thinking and response.
	Categorizing shopping list	Organizing a shopping list into categories quickly and efficiently.
Sustained attention	Jigsaw puzzles	Focusing on completing a puzzle over an extended period of time.
	Mandala coloring	Engaging in detailed and intricate coloring activities that require sustained focus.
	Bird watching	Observing birds and noting their behaviors for a prolonged period.
	Sorting lentils	Sorting different types of lentils or grains, requiring continuous attention to detail.
Divided attention	Mantra yoga	Practicing yoga while simultaneously chanting mantras, requiring focus on both physical and verbal tasks.
	Folding clothes with conversation	Engaging in a conversation while folding clothes, balancing attention between the task and the interaction.
Verbal fluency	"Name That Game"	Naming items in a category quickly (e.g., animals, fruits).
	Alphabet challenges	Generating words that start with each letter of the alphabet under time constraints.
	Word chains	Creating a chain of words where each new word starts with the last letter of the previous word.
Verbal working memory	Short stories with questions	Listening to short stories and answering questions about them to test retention and recall.
	Instruction relay	Following a series of instructions relayed verbally in sequence.
	Question chain	Answering a series of related questions where each response depends on recalling the previous question and answer.
Set shifting	Opposite word chain	Naming opposites of given words quickly (e.g., hot-cold, big-small).
	Sorting of lentils, objects, vegetables	Switching between different sorting criteria (e.g., by size, color, type) to practice cognitive flexibility.
Verbal learning & memory	Free recall	Recalling lists of words or items freely after a short delay.
	Review the day	Reviewing and recounting events of the day to enhance memory recall.
	Active listening	Engaging in conversations with active recall of details discussed.
Visual learning and logical memory	Object observation & drawing	Observing objects and then drawing them from memory to enhance visual recall.
	Spot the differences	Identifying differences between two similar pictures to practice visual discrimination and memory.
	Story sequencing	Arranging story elements or pictures in the correct sequence to improve logical memory and understanding of narrative structure.

- supporting her development of social skills (e.g., role-playing social interactions, practicing conversation starters);
- managing challenging behavior that might appear due to communication difficulties;
- setting clear and consistent expectations for communication within the family and VR.

Follow-up and outcomes

SUD were assessed at the beginning of each session using a 0–100 scale, where 0 represents no distress and 100 represents maximum distress (Figure 2). VR was asked to rate patient overall emotional distress level related to her TBI symptoms and daily functioning ability. This provided a consistent measure of her perceived stress levels throughout the treatment process. After a gap of two sessions, SUD was taken from VR. Initially it stood at 90 at baseline. After follow up 1, which corresponded to the 4th session, it was reported to be 85, an indication of slight improvement. This continued until the next follow up of SUD. Despite the slight improvement after the second follow up, there was a minor increase to 88 in the third follow up session of SUD. Thus, the reasons for that were explored and alternate therapy approaches were also explored, ranging from the cognitive-behavioral approach to a combination of REBT and CFT. In the next 4th follow up

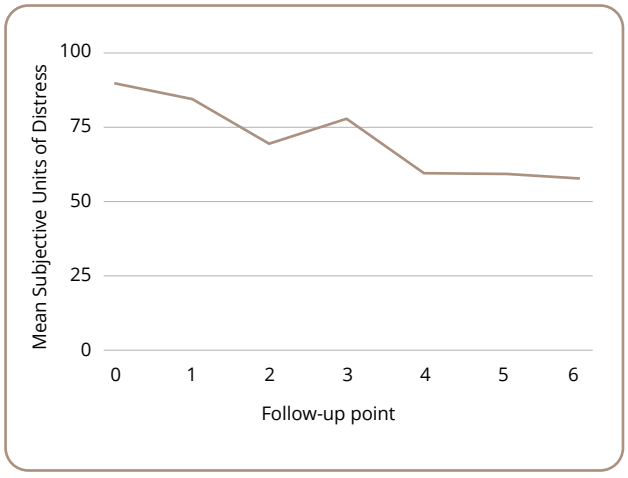

Figure 2. Mean Subjective Units of Distress according to the consequent follow-ups.

Source: Mahajan et al., 2024.

session of SUD, it had fallen to 60 and remained there until the next session, which suggests that the exercises and interventions tailored to the patient's cognitive capacities may have had a more substantial reduction impact on the distress levels. The sessions focused on challenging irrational beliefs, self-compassion imagery, and daily diary writing. In the last follow-up session after two therapy sessions, SUD was reported to be 58 out of the 100, which highlights the possible positive impact of the intervention and psychotherapeutic sessions on the patient.

Timeline

The patient timeline is presented in Table 3.

DISCUSSION

Clinical case summary

The present case report of TBI highlights the importance of a comprehensive psychotherapeutic approach, especially when psychotherapeutic management is not readily available, whether in a global or Indian context. Thus, this case report adds to the existing literature by addressing the existing gap through the application of integrated psychotherapeutic modules and finding them suggestively

Table 3. Patient VR chronology of disease development, key events and prognosis

Time period	Key events	Condition
Pre-accident	Completed post-graduate degree. Started working in professional roles.	Normal development, above-average student.
Year 0	The patient was in a serious accident, suffered head injury. In coma for nearly a month.	Bedridden, assisted self-care, crying, limited communication.
Year 0+6 months	Moved to spouse's family home.	Slight improvement: could eat independently, walk and talk a little. Experienced sadness, anger, suicidal thoughts. Difficulty adjusting due to cultural and economic differences.
Year 1	Returned to parental home.	
Year 2	Divorced by first spouse due to interpersonal issues and behavioral changes. Lost job.	Experienced feelings of loneliness, shame, and self-blame.
Years 2–5	Gradual physical recovery at home. Started helping with house chores and minor purchases.	Persistent low mood and worry about the future.
Year 5–8	Entered second marriage.	Experienced difficulty in establishing relationship due to educational differences. Continued feelings of low mood and increased irritability.
Year 8 (6 months prior to the assessment)	Estranged from second spouse due to interpersonal problems. On the verge of second divorce. Began psychotherapeutic treatment and pharmacotherapy.	
Current status (at time of the assessment)		Ongoing psychological concerns: • forgetfulness; • difficulty walking; • irritability; • guilt and shame; • low mood; • undergoing treatment.

effective based on a single case study, because the overall tendency seems to be to focus on surgical intervention and the management of psychiatric disorders and the implications of TBI but less on psychotherapeutic work.

Summary interpretation of the results

According to existing research, TBI survivors often face multifaceted challenges that can range from sensory problems to cognitive deficits and personality changes [21]. However, from the perspective of gender studies, women, especially, may encounter unique challenges due to gender roles and societal expectations, as well as physiological changes which are nonexistent in men [22]. This was the scenario in the case of patient VR, wherein the challenges faced by her were exacerbated by cultural-societal pressures and a history of high parental expectations, which led to emotional distress and internalized stress. This was the fallout that was addressed in the sessions exploring how the cultural and societal expectations had become integral to her identity and recovery process.

Additionally, in her case, establishing a trusting and collaborative therapeutic alliance was key. According to the literature, a therapeutic alliance which is collaborative in nature plays an important role in improving outcomes for individual patients with TBI[2].

The therapeutic results indicate the effectiveness of this combined approach. VR showed improvements in the ability to function daily, emotional management, and cognitive capacities. This is consistent with studies that argue for an integral approach to therapy after a brain injury, to accommodate the specific needs of patients [23].

This case emphasizes the importance of comprehensive neurorehabilitation programs that incorporate psychological therapies into cognitive rehabilitation. This holistic approach can help patients live meaningful lives despite their injuries. Therapists dealing with patients who have suffered a TBI should appreciate their patients' strengths, accept their new limitations, and be prepared to deal with the emotional issues that are inherent in such cases [24], which in turn highlights the need to train mental health professionals in that direction.

Practical constraints, such as a dearth of skilled experts and excessive caseloads, must be addressed in order to be able to offer adequate care to patients. Future considerations should focus on designing, conducting, and implementing programs that train therapists to work efficiently in the area of neurorehabilitation. The available body of research underscores the importance of tailoring a variety of therapeutic modalities to meet the unique needs of each individual patient [25]. It has been shown that multimodal therapies can significantly enhance the quality of life of survivors of TBI [26]. This evidence highlights the effectiveness of a personalized approach that takes into account cultural and gender differences, leading to substantial improvement in outcomes for patients.

This case report contributes to the growing body of evidence supporting the use of holistic and patient-centered methods in TBI rehabilitation [26]. It underscores the importance of a comprehensive psychotherapeutic approach in managing TBI. VR's case adds to existing literature by demonstrating the efficacy that comes with integrating CR into REBT and CFT. Because of the preference of surgical and pharmacological interventions in TBI, psychotherapeutic management remains underrepresented, particularly in India [27–30][3].

The therapeutic approach has played a crucial role in VR's progress, aligning with research indicating that a collaborative relationship improves outcomes for TBI patients[3]. VR showed significant improvements in daily functioning, emotional regulation, and cognitive abilities, supporting the case for the effectiveness of a holistic and personalized therapeutic approach [23]. VR's attitude towards this comprehensive approach was assessed through clinical interviews and SUD. She reported feeling more able to engage and understanding compared to previous treatments, noting that addressing both the cognitive and emotional aspects of TBI simultaneously felt more reasonable. VR expressed particular appreciation for the self-compassion elements of CFT.

This case highlights the necessity for comprehensive neurorehabilitation programs that incorporate psychological therapies, alongside cognitive rehabilitation. Future efforts should focus on training mental health professionals in neurorehabilitation and designing multimodal therapeutic intervention protocols that are tailored to individual needs.

In conclusion, the integration of REBT, CFT, and CR in the treatment of TBI demonstrates the potential for improving recovery and quality of life. This holistic approach

[2] Available from: https://www.tbimedslp.com/blog/traumatic-brain-injury-rehabilitation

[3] Available from: https://newsroom.uw.edu/news-releases/collaborative-care-model-reduces-tbi-pain-study-shows

addresses the intricate interplay of cognitive, emotional, and behavioral challenges, emphasizing the need for personalized care in TBI rehabilitation.

Future efforts should include a reassessment of the NIMHANS Neuropsychological Battery of tests used to assess patient improvements in order to produce parametric data that allow for assessing the dynamics of a patient's condition, confirming the advantages of this comprehensive approach in the treatment of patient objectively.

When juxtaposed with our initial aim, this case study has allowed us to achieve significant progress while also highlighting areas for future research. Our efforts have contributed to addressing the gap in the literature on the comprehensive psychotherapeutic management of TBI in the Indian context, though more research is needed. This case has successfully demonstrated the potential benefits of a holistic, patient-centered approach that takes into account cognitive limitations, cultural factors, and individual needs. The integration of REBT, CFT, and CR shows promising results in efforts to improve emotional regulation, cognitive functioning, and quality of life for patients with TBI, in line with our aim to explore the synergistic effects of combined therapies. This case adds to the growing body of evidence that supports integrative approaches in neurorehabilitation, emphasizing the importance of combining psychological interventions with cognitive rehabilitation. It effectively highlights the value of flexible, tailored interventions that address both the cognitive and emotional aspects of TBI recovery, while providing valuable insights into the practical application of an integrated approach and laying the groundwork for future studies. This case study also underscores the need for large-scale, quantitative research to more definitively demonstrate the efficacy of this approach in TBI rehabilitation.

Limitations

As the authors of this case report, we acknowledge several limitations in our work. Our single-case design, while providing valuable insights, limits any generalization to the broader TBI population. We relied primarily on SUD for outcome measurement, which, although clinically useful, lacks the objectivity of standardized measures. Our report would have benefited from more comprehensive pre- and post-intervention neuropsychological assessments to objectively quantify cognitive improvement. We also recognize the absence of long-term follow-up data, which could have demonstrated the durability of the observed improvements. Despite these limitations, we believe our case report offers valuable insights into an integrated approach for TBI rehabilitation, laying the groundwork for future, more rigorous studies in this area.

CONCLUSION

This case report demonstrates a successful integration of REBT, CFT, and TBI. The holistic, personalized approach effectively addressed the multifaceted psychological and cognitive challenges faced by the patient, promoting recovery and enhancing her quality of life. These findings underscore the importance of incorporating diverse therapeutic modalities in TBI management and highlight the need for further research and adoption of such approaches in clinical practice.

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