REVIEW

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

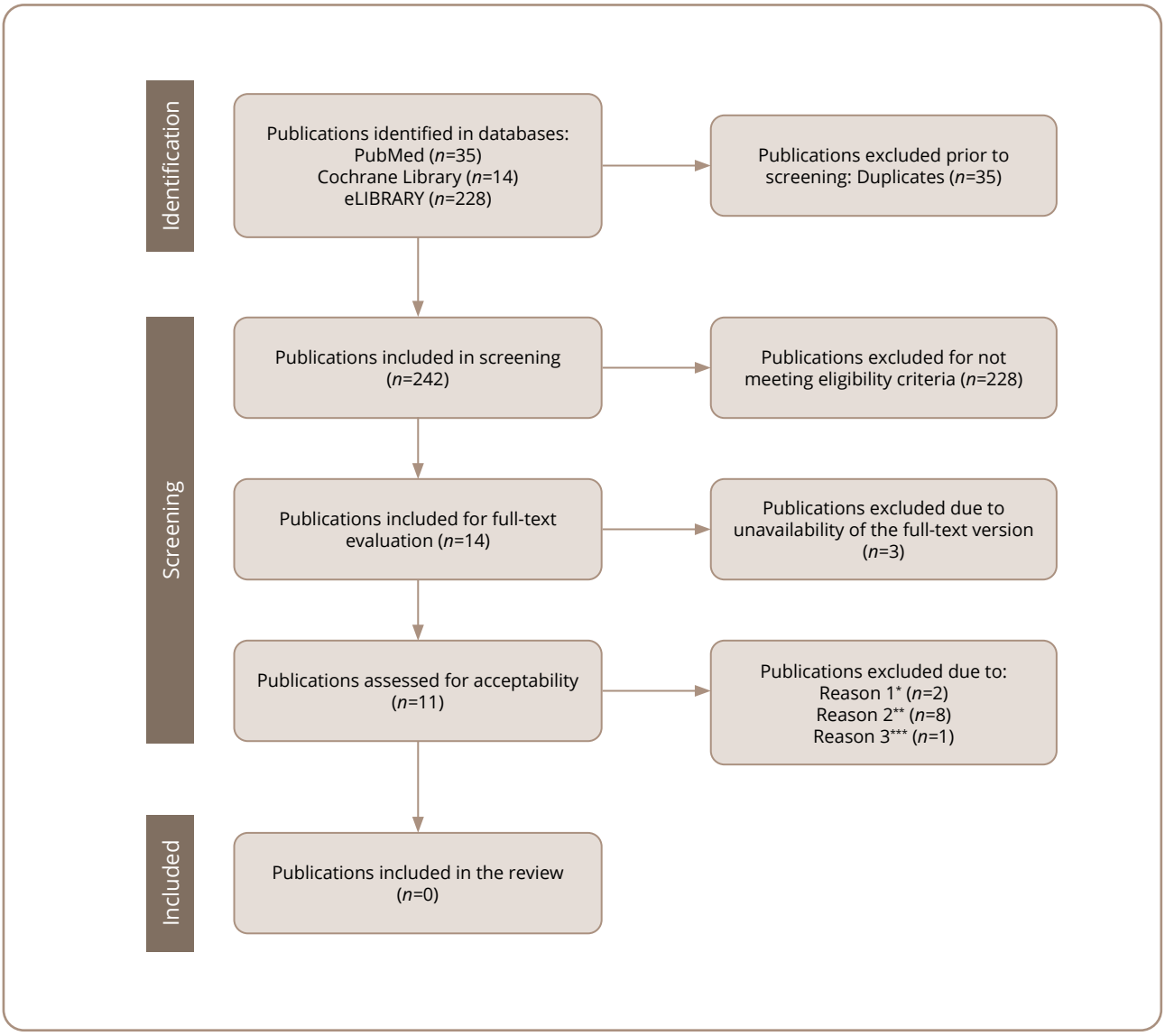


Figure 1. PRISMA flow chart demonstrating the selection process of comorbid depression and alcohol abuse studies.

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

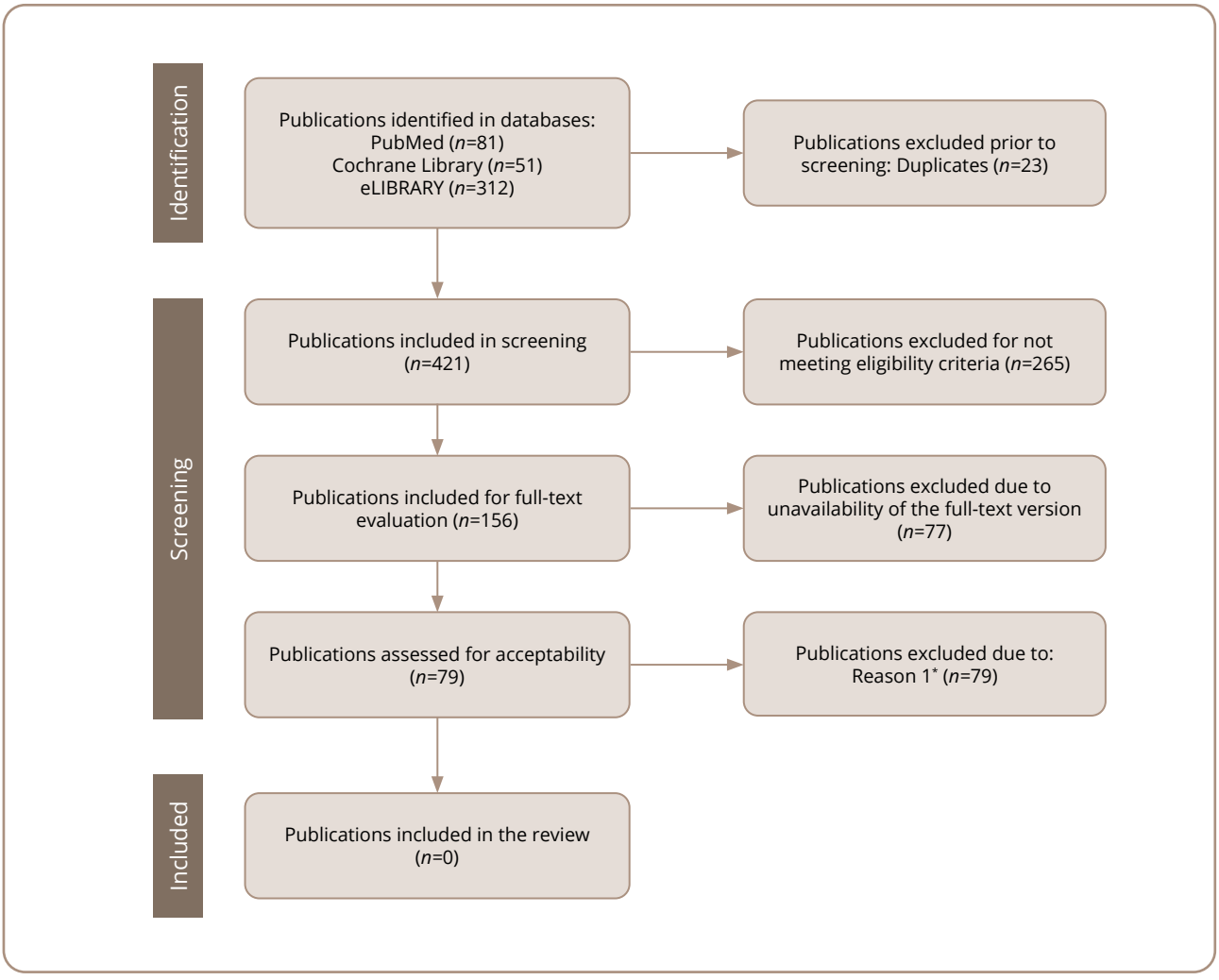


Figure 2. Flow chart demonstrating the selection process of comorbid depression and anxiety disorders studies.

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

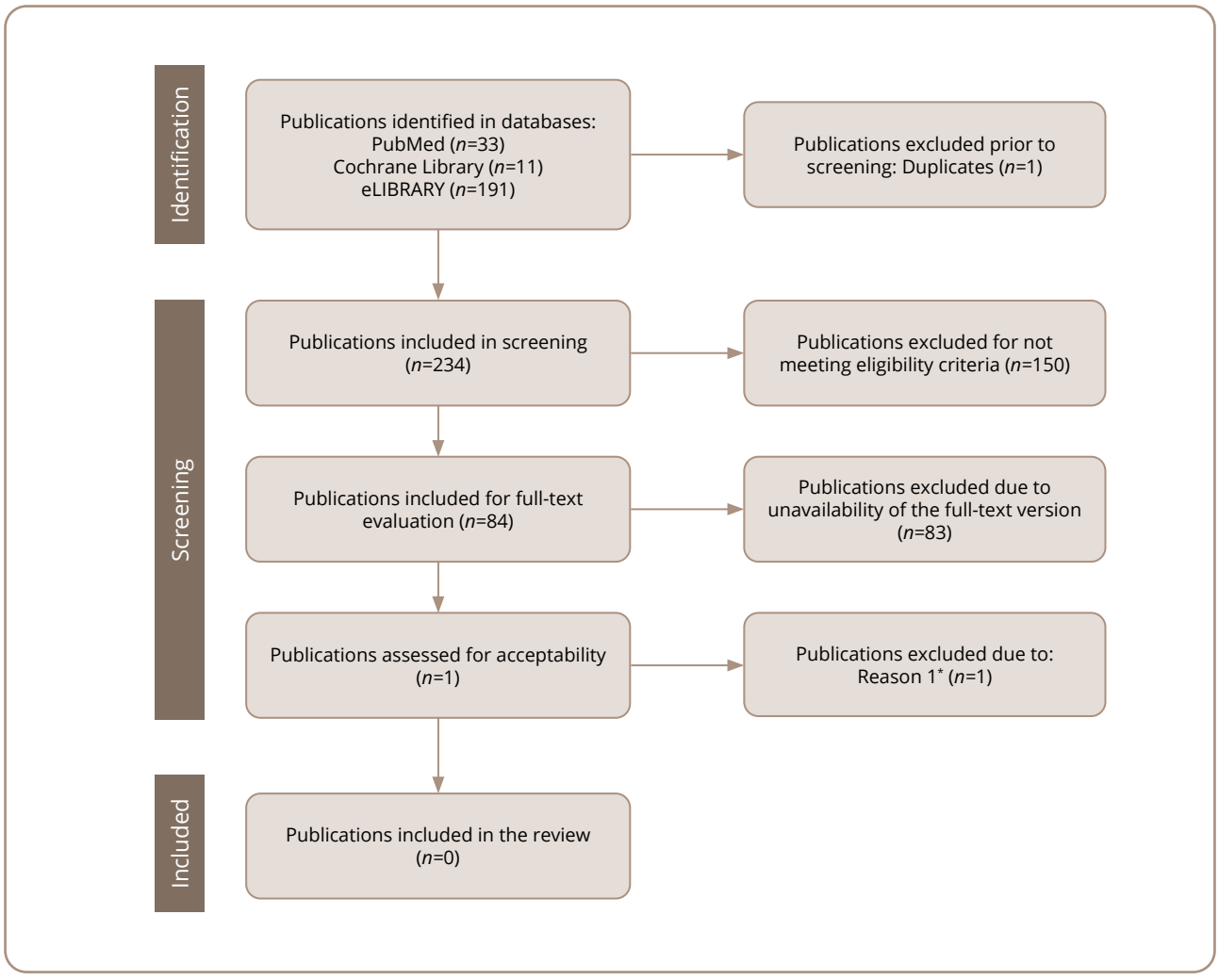


Figure 3. Flow chart demonstrating the selection process of comorbid depression and epilepsy studies.

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.

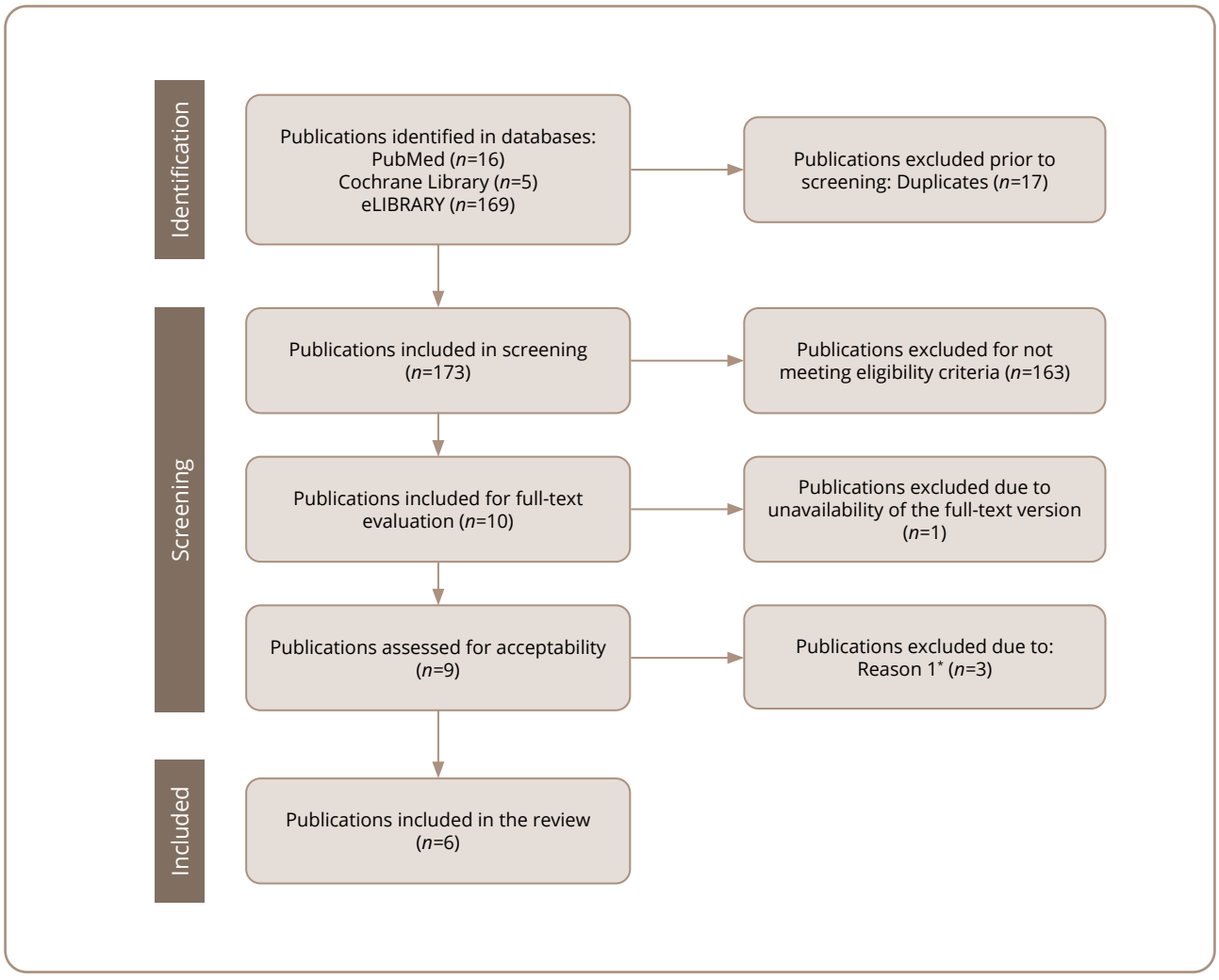


Figure 4. Flow chart demonstrating the selection process of comorbid depression and Parkinson's disease studies.

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].

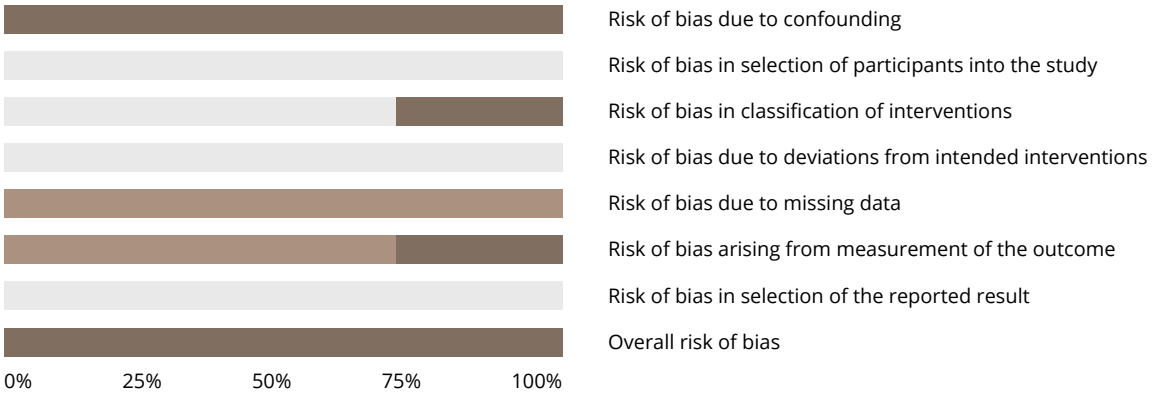
In the study with a control group [134], the randomization procedures and participant allocation were not specified, so we assessed the risk of bias as for non-randomized studies. We found the methodological quality of the included studies to be low (Figure 5).

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
Table S3: https://doi.org/10.17816/CP15560-145410
Table S4: https://doi.org/10.17816/CP15560-145411

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References

1. Evans-Lacko S, Aguilar-Gaxiola S, Al-Hamzawi A, et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: results from the WHO World Mental Health (WMH) surveys. Psychol Med. 2018;48(9):1560–1571. doi: 10.1017/S0033291717003336
2. Santomauro DF, Mantilla Herrera AM, Shadid J, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet. 2021;398(10312):1700–1712. doi: 10.1016/S0140-6736(21)02143-7
3. Arnaud AM, Brister TS, Duckworth K, et al. Impact of Major Depressive Disorder on Comorbidities: A Systematic Literature Review. J Clin Psychiatry. 2022;83(6) :21r14328. doi: 10.4088/JCP.21r14328
4. McGrath JJ, Lim CCW, Plana-Ripoll O, et al. Comorbidity within mental disorders: a comprehensive analysis based on 145 990 survey respondents from 27 countries. Epidemiol Psychiatr Sci. 2020;29:e153. doi: 10.1017/S2045796020000633
5. Zimmerman M, Chelminski I, McDermut W. Major Depressive Disorder and Axis I Diagnostic Comorbidity. J Clin Psychiatry. 2002;63(3):187–193. doi: 10.4088/JCP.v63n0303
6. Rhee YJ, Gustafson M, Ziffra M, et al. Association of Comorbidity with Depression Treatment Adequacy among Privately Insured Patients Initiating Depression Treatment. Open J Depress. 2015;04(02):13–23. doi: 10.4236/ojd.2015.42002
7. Arnaud AM, Brister TS, Duckworth K, et al. Impact of Treating Depression on Associated Comorbidities: A Systematic Literature Review. Prim Care Companion CNS Disord. 2023;25(1):22r03330. doi: 10.4088/PCC.22r03330
8. Bennabi D, Yrondi A, Charpeaud T, et al. Clinical guidelines for the management of depression with specific comorbid psychiatric conditions French recommendations from

experts (the French Association for Biological Psychiatry and Neuropsychopharmacology and the foundation FondaMental). BMC Psychiatry. 2019;19(1):50. doi: 10.1186/s12888-019-2025-7
9. Charrier A, Olliac B, Roubertoux P, et al. Clock Genes and Altered Sleep–Wake Rhythms: Their Role in the Development of Psychiatric Disorders. Int J Mol Sci. 2017;18(5):938. doi: 10.3390/ijms18050938
10. Chellappa SL, Schröder C, Cajochen C. Chronobiology, excessive daytime sleepiness and depression: Is there a link? Sleep Med. 2009;10(5):505–514. doi: 10.1016/j.sleep.2008.05.010
11. Dollish HK, Tsyglakova M, McClung CA. Circadian rhythms and mood disorders: Time to see the light. Neuron. 2024;112(1):25–40. doi: 10.1016/j.neuron.2023.09.023
12. Srinivasan V, Pandi-Perumal SR, Trakht I, et al. Pathophysiology of depression: role of sleep and the melatonergic system. Psychiatry Res. 2009;165(3):201–214. doi: 10.1016/j.psychres.2007.11.020
13. Hickie IB, Rogers NL. Novel melatonin-based therapies: potential advances in the treatment of major depression. Lancet. 2011;378(9791):621–631. doi: 10.1016/S0140-6736(11)60095-0
14. Mosolov SN. [Current biological hypotheses of recurrent depression (review)]. Zhurnal nevrologii i psihiatrii im. S.S. Korsakova. 2012;112(11 Pt2):29–40. Russian.
15. De Berardis D, Marini S, Fornaro M, et al. The melatonergic system in mood and anxiety disorders and the role of agomelatine: implications for clinical practice. Int J Mol Sci. 2013;14(6):12458–12483. doi: 10.3390/ijms140612458
16. Zaki NFW, Spence DW, BaHammam AS, et al. Chronobiological theories of mood disorder. Eur Arch Psychiatry Clin Neurosci. 2018;268(2):107–118. doi: 10.1007/s00406-017-0835-5
17. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord. 2011;135(1-3):10–19. doi: 10.1016/j.jad.2011.01.011
18. Chan JWY, Lam SP, Li SX, et al. Eveningness and Insomnia: Independent Risk Factors of Nonremission in Major Depressive Disorder. Sleep. 2014;37(5):911–917. doi: 10.5665/sleep.3658
19. Strelnik SN, Romanov DV. [Chronobiological approach to depressive disorders therapy]. Rossijskij psihiatricheskij zhurnal. 2008;(6):84–89. Russian.
20. Boiko DI, Shkodina AD, Hasan MM, et al. Melatonergic Receptors (Mt1/Mt2) as a Potential Additional Target of Novel Drugs for Depression. Neurochem Res. 2022;47(10):2909–2924. doi: 10.1007/s11064-022-03646-5
21. Cardinali DP, Srinivasan V, Brzezinski A, et al. Melatonin and its analogs in insomnia and depression. J Pineal Res. 2012;52(4):365–375. doi: 10.1111/j.1600-079X.2011.00962.x
22. Catena-Dell'Osso M, Marazziti D, Rotella F, et al. Emerging Targets for the Pharmacological Treatment of Depression: Focus on Melatonergic System. Curr Med Chem. 2012;19(3):428–437. doi: 10.2174/092986712803414277
23. Hardeland R, Poeggeler B, Srinivasan V, et al. Melatonergic Drugs in Clinical Practice. Arzneimittelforschung. 2011;58(1):1–10. doi: 10.1055/s-0031-1296459
24. Aykan U, Güvel MC, Paykal G, et al. Neuropharmacologic modulation of the melatonergic system. Explor Neurosci. 2023;2(6):287–306. doi: 10.37349/en.2023.00029
25. Dubovsky SL, Warren C. Agomelatine, a melatonin agonist with antidepressant properties. Expert Opin Investig Drugs. 2009;18(10):1533–1540. doi: 10.1517/13543780903292634
26. Fuchs E, Simon M, Schmelting B. Pharmacology of a new antidepressant: benefit of the implication of the melatonergic system. Int Clin Psychopharmacol. 2006;21 (Suppl 1):S17–S20. doi: 10.1097/01.yic.0000199456.39552.c7
27. Syunyakov TS. [Effects of fluvoxamine on the melatonin levels: literature overview and possible clinical implication]. Psihiatrija i psihofarmakoterapija. 2014;16(1):38–43. Russian.
28. Härtter S, Wang X, Weigmann H, et al. Differential Effects of Fluvoxamine and Other Antidepressants on the Biotransformation of Melatonin. J Clin Psychopharmacol. 2001;21(2):167–174. doi: 10.1097/00004714-200104000-00008
29. Hermesh H, Lemberg H, Abadi J, et al. Circadian Rhythm Sleep Disorders as a Possible Side Effect of Fluvoxamine. CNS Spectr. 2001;6(6):511–513. doi: 10.1017/S1092852900008051
30. Hao Y, Hu Y, Wang H, et al. The Effect Of Fluvoxamine On Sleep Architecture Of Depressed Patients With Insomnia: An 8-Week, Open-Label, Baseline-Controlled Study. Nat Sci Sleep. 2019;11:291–300. doi: 10.2147/NSS.S220947
31. Hunt GE, Malhi GS, Lai HMX, et al. Prevalence of comorbid substance use in major depressive disorder in community and clinical settings, 1990–2019: Systematic review and meta-analysis. J Affect Disord. 2020;266:288–304. doi: 10.1016/j.jad.2020.01.141
32. Sullivan LE, Fiellin DA, O'Connor PG. The prevalence and impact of alcohol problems in major depression: A systematic review. Am J Med. 2005;118(4):330–341. doi: 10.1016/j.amjmed.2005.01.007
33. Kurhaluk N. Alcohol and melatonin. Chronobiol Int. 2021;38(6):785–800. doi: 10.1080/07420528.2021.1899198
34. Holma M, Holma I, Isometsä E. Comorbid alcohol use disorder in psychiatric MDD patients: A five-year prospective study. J Affect Disord. 2020;267:283–288. doi: 10.1016/j.jad.2020.02.024
35. Calarco CA, Lobo MK. Depression and substance use disorders: Clinical comorbidity and shared neurobiology. Int Rev Neurobiol. 2020;157:245–309. doi: 10.1016/bs.irn.2020.09.004
36. Swendsen JD, Merikangas KR. The comorbidity of depression and substance use disorders. Clin Psychol Rev. 2000;20(2):173–189. doi: 10.1016/S0272-7358(99)00026-4
37. Burns L, Teesson M, O'Neill K. The impact of comorbid anxiety and depression on alcohol treatment outcomes. Addiction. 2005;100(6):787–796. doi: 10.1111/j.1360-0443.2005.001069.x
38. Das A, Prithviraj M, Mohanraj PS. Role of Melatonin in the Management of Substance Addiction: A Systematic Review. Cureus. 2022;14(7):e26764. doi: 10.7759/cureus.26764.
39. Li J, Wang H, Li M, et al. Efficacy of pharmacotherapeutics for patients comorbid with alcohol use disorders and depressive symptoms — A bayesian network meta-analysis. CNS Neurosci Ther. 2020;26(11):1185–1197. doi: 10.1111/cns.13437.
40. Essau CA. Chapter 11 – Comorbidity of addictive problems: assessment and treatment implications. In: Essau CA, Delfabbro PH, editors. Adolescent addiction: epidemiology, assesment and treatment. 2nd edition. San Diego: Academic Press; 2020. p. 291–317.
41. First MB. Mutually exclusive versus co-occurring diagnostic categories: the challenge of diagnostic comorbidity. Psychopathology. 2005;38(4):206–210. doi: 10.1159/000086093
42. Torrens M, Fonseca F, Mateu G, et al. Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. Drug Alcohol Depend. 2005;78(1):1–22. doi: 10.1016/j.drugalcdep.2004.09.004
43. Tseng I, Ganz A, Mitton AG, et al. Comorbidity of Alcohol Use Disorder and Depression: A Case Report and Review of the Literature. Addict Disord Their Treat. 2017;16(3):121–128. doi: 10.1097/ADT.0000000000000106

44. Meyrel M, Rolland B, Geoffroy PA. Alterations in circadian rhythms following alcohol use: A systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2020;99:109831. doi: 10.1016/j.pnpbp.2019.109831
45. Burgess HJ, Troost JP, Rizvydeen M, et al. Do sleep and circadian characteristics predict alcohol use in adult drinkers? Alcohol Clin Exp Res (Hoboken). 2024;48(4):680–691. doi: 10.1111/acer.15280
46. Hisler GC, Rothenberger SD, Clark DB, et al. Is there a 24-hour rhythm in alcohol craving and does it vary by sleep/circadian timing? Chronobiol Int. 2021;38(1):109–121. doi: 10.1080/07420528.2020.1838532
47. Lamers F, Van Oppen P, Comijs HC, et al. Comorbidity Patterns of Anxiety and Depressive Disorders in a Large Cohort Study: the Netherlands Study of Depression and Anxiety (NESDA). J Clin Psychiatry. 2011;72(3):341–348. doi: 10.4088/JCP.10m06176blu
48. Melartin TK, Rytsälä HJ, Leskelä US, et al. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. J Clin Psychiatry. 2002;63(2):126–134.
49. Moffitt TE, Harrington H, Caspi A, et al. Depression and Generalized Anxiety Disorder: Cumulative and Sequential Comorbidity in a Birth Cohort Followed Prospectively to Age 32 Years. Arch Gen Psychiatry. 2007;64(6):651–660. doi: 10.1001/archpsyc.64.6.651
50. de Graaf R, ten Have M, Tuithof M, et al. First-incidence of DSM-IV mood, anxiety and substance use disorders and its determinants: results from the Netherlands Mental Health Survey and Incidence Study-2. J Affect Disord. 2013;149(1-3):100–107. doi: 10.1016/j.jad.2013.01.009
51. Radionov DS, Karavayeva TA, Vasilyeva AV, et al. [Peculiarities of alcohol abuse by individuals with neurotic spectrum anxiety disorders. Clinical aspects and issues of psychotherapy]. Voprosy narkologii. 2023;35(3):27–50. Russian.
52. Klimanova SG, Berezina AA, Trusova AV, et al. [The relationship between clinical characteristics of patients with alcohol use disorder and drinking motives]. Obozrenie psihiatrii i medicinskoj psihologii imeni V.M. Behtereva. 2022;56(4):63–76. Russian. doi: 10.31363/2313-7053-2022-4-63-76
53. Hovens JGFM, Giltay EJ, Wiersma JE, et al. Impact of childhood life events and trauma on the course of depressive and anxiety disorders. Acta Psychiatr Scand. 2012;126(3):198–207. doi: 10.1111/j.1600-0447.2011.01828.x
54. Choi KW, Kim YK, Jeon HJ. Comorbid Anxiety and Depression: Clinical and Conceptual Consideration and Transdiagnostic Treatment. Adv Exp Med Biol. 2020;1191:219–235. doi: 10.1007/978-981-32-9705-0_14
55. Liu Y, Zhao J, Guo W. Emotional Roles of Mono-Aminergic Neurotransmitters in Major Depressive Disorder and Anxiety Disorders. Front Psychol. 2018;9:2201. doi: 10.3389/fpsyg.2018.02201
56. van Balkom AJ, van Boeijen CA, Boeke AJ, et al. Comorbid depression, but not comorbid anxiety disorders, predicts poor outcome in anxiety disorders. Depress Anxiety. 2008;25(5):408–415. doi: 10.1002/da.20386
57. Difrancesco S, Lamers F, Riese H, et al. Sleep, circadian rhythm, and physical activity patterns in depressive and anxiety disorders: A 2-week ambulatory assessment study. Depress Anxiety. 2019;36(10):975–986. doi: 10.1002/da.22949
58. Difrancesco S, Penninx BWJH, Riese H, et al. The role of depressive symptoms and symptom dimensions in actigraphy-assessed sleep, circadian rhythm, and physical activity. Psychol Med. 2022;52(13):2760–2766. doi: 10.1017/S0033291720004870
59. Üzer A, Kurtses Gürsoy B. The mediating roles of depression, anxiety, and psychological pain in the relationship between chronotype and suicide in patients with depressive disorder. Chronobiol Int. 2022;39(10):1352–1358. doi: 10.1080/07420528.2022.2108438
60. Stein DJ. Evidence-Based Pharmacotherapy of Anxiety Symptoms in Patients with Major Depressive Disorder: Focus on Agomelatine. Neurol Ther. 2023;12(Suppl 1):13–19. doi: 10.1007/s40120-023-00470-z
61. Guaiana G, Gupta S, Chiodo D, et al. Agomelatine versus other antidepressive agents for major depression. Cochrane Database Syst Rev. 2013;(12):CD008851. doi: 10.1002/14651858.CD008851
62. Rausch JL, Hobby HM, Shendarkar N, et al. Fluvoxamine treatment of mixed anxiety and depression: evidence for serotonergically mediated anxiolysis. J Clin Psychopharmacol. 2001;21(2):139–42. doi: 10.1097/00004714-200104000-00004
63. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. Lancet Neurol. 2016;15(1):106–115. doi: 10.1016/S1474-4422(15)00225-2
64. Nobili L, Frauscher B, Eriksson S, et al. Sleep and epilepsy: A snapshot of knowledge and future research lines. J Sleep Res. 2022;31(4):e13622. doi: 10.1111/jsr.13622.
65. Moore JL, Carvalho DZ, St Louis EK, et al. Sleep and Epilepsy: a Focused Review of Pathophysiology, Clinical Syndromes, Co-morbidities, and Therapy. Neurotherapeutics. 2021;18(1):170–180. doi: 10.1007/s13311-021-01021-w
66. Banach M, Gurdziel E, Jędrych M, et al. Melatonin in experimental seizures and epilepsy. Pharmacol Rep. 2011;63(1):1–11. doi: 10.1016/s1734-1140(11)70393-0
67. Andrew T, Milinis K, Baker G, et al. Self reported adverse effects of mono and polytherapy for epilepsy. Seizure. 2012;21(8):610–613. doi: 10.1016/j.seizure.2012.06.013
68. Joshi R, Tripathi M, Gupta P, et al. Adverse effects & drug load of antiepileptic drugs in patients with epilepsy: Monotherapy versus polytherapy. Indian J Med Res. 2017;145(3):317–326. doi: 10.4103/ijmr.IJMR_710_15
69. Zelano J, Nika O, Asztely F, et al. Prevalence and nature of patient-reported antiseizure medication side effects in a Swedish regional multi-center study. Seizure. 2023;113:23–27. doi: 10.1016/j.seizure.2023.10.016
70. Maghbooli M, Alyan NajafAbadi S, MalekMahmoudi G, et al. Effect of add-on melatonin on seizure outcomes and quality of sleep in epilepsy with idiopathic generalized tonic-clonic seizures alone in adult patients: Cross-sectional, randomized, double-blind, placebo-controlled clinical trial. Brain Behav. 2023;13(2):e2860. doi: 10.1002/brb3.2860
71. Brigo F, Igwe SC, Del Felice A. Melatonin as add-on treatment for epilepsy. Cochrane Database Syst Rev. 2016;2016(8):CD006967. doi: 10.1002/14651858.CD006967.pub4
72. Schrag A, Taddei RN. Depression and Anxiety in Parkinson's Disease. Int Rev Neurobiol. 2017:133:623–655. doi: 10.1016/bs.irn.2017.05.024
73. Fils JM, Penick EC, Nickel EJ, et al. Minor versus major depression: a comparative clinical study. Prim Care Companion J Clin Psychiatry. 2010;12(1):PCC.08m00752. doi: 10.4088/PCC.08m00752blu
74. Tandberg E, Larsen JP, Aarsland D, et al. The occurrence of depression in Parkinson's disease. A community-based study. Arch Neurol. 1996;53(2):175–179. doi: 10.1001/archneur.1996.00550020087019
75. Wermuth L. A double-blind, placebo-controlled, randomized, multi-center study of pramipexole in advanced Parkinson's

disease. Eur J Neurol. 1998;5(3):235–242. doi: 10.1046/j.1468-1331.1998.530235.x
76. Hart LL, Middleton RK, Wandres DL. Depression treatment in Parkinson's disease. DICP, The Annals of Pharmacotherapy. 1991;25:137–138.
77. Gómez-Esteban JC, Tijero B, Somme J, et al. Impact of psychiatric symptoms and sleep disorders on the quality of life of patients with Parkinson's disease. J Neurol. 2011;258(3):494-499. doi: 10.1007/s00415-010-5786-y
78. Hoogendijk WJ, Sommer IE, Tissingh G, et al. Depression in Parkinson's disease. The impact of symptom overlap on prevalence. Psychosomatics. 1998;39(5):416–421. doi: 10.1016/S0033-3182(98)71300-3
79. Reijnders JS, Ehrt U, Weber WE, et al. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2008;23(2):183–189. doi: 10.1002/mds.21803
80. Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry. 1992;149(4):443–454. doi: 10.1176/ajp.149.4.443
81. Shabnam GN, Th C, Kho D, et al. Therapies for depression in Parkinson's disease. Cochrane Database Syst Rev. 2003;(3):CD003465. doi: 10.1002/14651858.CD003465
82. Hantz P, Caradoc-Davies G, Caradoc-Davies T, et al. Depression in Parkinson's disease. Am J Psychiatry. 1994;151(7):1010–1014. doi: 10.1176/ajp.151.7.1010
83. Marsh L. Neuropsychiatric aspects of Parkinson's disease. Psychosomatics. 2000;41(1):15–23. doi: 10.1016/S0033-3182(00)71169-8
84. Richard IH, Kurlan R. A survey of antidepressant drug use in Parkinson's disease. Parkinson Study Group. Neurology. 1997;49(4):1168–1170. doi: 10.1212/wnl.49.4.1168
85. Weintraub D, Moberg PJ, Duda JE, et al. Recognition and treatment of depression in Parkinson's disease. J Geriatr Psychiatry Neurol. 2003;16(3):178–183. doi: 10.1177/0891988703256053
86. Weintraub D, Morales KH, Moberg PJ, et al. Antidepressant studies in Parkinson's disease: a review and meta-analysis. Mov Disord. 2005;20(9):1161–1169. doi: 10.1002/mds.20555
87. Chen JJ, Marsh L. Depression in Parkinson's disease: identification and management. Pharmacotherapy. 2013;33(9):972–983. doi: 10.1002/phar.1314
88. Creed F, Dickens C. Depression in the medically ill. In: Steptoe A, editor. Depression and physical illness. New York: Cambridge University Press; 2007. p. 3–10.
89. Remy P, Doder M, Lees A, et al. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain. 2005;128(Pt 6):1314–1322. doi: 10.1093/brain/awh445
90. Lesage S, Belarbi S, Troiano A, et al. Is the common LRRK2 G2019S mutation related to dyskinesias in North African Parkinson disease? Neurology. 2008;71(19):1550–1552. doi: 10.1212/01.wnl.0000338460.89796.06
91. Belarbi S, Hecham N, Lesage S, et al. LRRK2 G2019S mutation in Parkinson's disease: a neuropsychological and neuropsychiatric study in a large Algerian cohort. Parkinsonism Relat Disord. 2010;16(10):676–679. doi: 10.1016/j.parkreldis.2010.09.003
92. Karlsen KH, Larsen JP, Tandberg E, et al. Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999;66(4):431–435. doi: 10.1136/jnnp.66.4.431
93. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry. 2000;69(3):308–312. doi: 10.1136/jnnp.69.3.308
94. Weintraub D, Moberg PJ, Duda JE, et al. Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. J Am Geriatr Soc. 2004;52(5):784–788. doi: 10.1111/j.1532-5415.2004.52219.x
95. Menza M, Dobkin RD, Marin H, et al. A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology. 2009;72(10):886–892. doi: 10.1212/01.wnl.0000336340.89821.b3
96. Global Parkinson's Disease Survey (GPDS) Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov Disord. 2002;17(1):60–67. doi: 10.1002/mds.10010
97. Asadpoordezaki Z, Coogan AN, Henley BM. Chronobiology of Parkinson's disease: Past, present and future. Eur J Neurosci. 2023;57(1):178–200. doi: 10.1111/ejn.15859
98. Gros P, Videnovic A. Sleep and circadian rhythm disorders in Parkinson's disease. Curr Sleep Med Rep. 2017;3(3):222–234. doi: 10.1007/s40675-017-0079-y
99. Mizrahi-Kliger AD, Kaplan A, Israel Z, et al. Entrainment to sleep spindles reflects dissociable patterns of connectivity between cortex and basal ganglia. Cell Rep. 2022;40(12):111367. doi: 10.1016/j.celrep.2022.111367
100. Nobre B, Rocha I, Morin CM, et al. Insomnia and circadian misalignment: an underexplored interaction towards cardiometabolic risk. Sleep Sci. 2021;14(1):55–63. doi: 10.5935/1984-0063.20200025
101. Breen DP, Nombela C, Vuono R, et al. Hypothalamic volume loss is associated with reduced melatonin output in Parkinson's disease. Mov Disord. 2016;31(7):1062–1066. doi: 10.1002/mds.26592
102. Li L, Zhao Z, Ma J, et al. Elevated Plasma Melatonin Levels Are Correlated With the Non-motor Symptoms in Parkinson's Disease: A Cross-Sectional Study. Front Neurosci. 2020;14:505. doi: 10.3389/fnins.2020.00505
103. Adi N, Mash DC, Ali Y, et al. Melatonin MT1 and MT2 receptor expression in Parkinson's disease. Med Sci Monit. 2010;16(2):BR61–67.
104. Bordet R, Devos D, Brique S, et al. Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. Clin Neuropharmacol. 2003;26(2):65–72. doi: 10.1097/00002826-200303000-00005
105. Videnovic A, Noble C, Reid KJ, et al. Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson disease. JAMA Neurol. 2014;71(4):463–469. doi: 10.1001/jamaneurol.2013.6239
106. Chung TH, Deane KH, Ghazi-Noori S, et al. Systematic review of antidepressant therapies in Parkinson's disease. Parkinsonism Relat Disord. 2003;10(2):59–65. doi: 10.1016/s1353-8020(03)00108-1
107. Higgins JPT, Thomas J, Chandler J, et al, editors. Cochrane Handbook for Systematic Reviews of Interventions: version 6.4 (updated August 2023) [Internet]. Cochrane; 2023 [cited 2024 Jul 12]. Available from https://training.cochrane.org/handbook
108. Bramer WM, Rethlefsen ML, Kleijnen J, et al. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev. 2017;6(1):245. doi: 10.1186/s13643-017-0644-y
109. Purssell E, McCrae N. How to Perform a Systematic Literature Review: A Guide for Healthcare Researchers, Practitioners and Students [Internet]. Cham: Springer International Publishing; 2020 [cited 2024 Jul 12]. Available from: https://link.springer.com/10.1007/978-3-030-49672-2
110. Ungryanu TN, Zhamalieva LM, Grjibovski AM. [Brief recommendations on how to write and publish systematic reviews]. West Kazakhstan Medical journal. 2019;61(1):26–36. Russian.

111. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71
112. Pochinkova PA, Gorbatova MA, Narkevich AN, et al. [Updated brief recommendations on writing and presenting systematic reviews: what's new in PRISMA-2020 guidelines?]. Morskaja medicina. 2022;8(2):88–101. Russian. doi: 10.22328/2413-5747-2022-8-2-88-101
113. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. doi: 10.1136/bmj.i4919
114. Vinnikova MA, Severtsev VV, Komarov SD, et al. [Fluvoxamine in the treatment of depressive disorders in alcohol abuse: results of randomized open-label comparative study]. Zhurnal nevrologii i psihiatrii im. S.S. Korsakova. 2021;121(12):57–62. Russian. doi: 10.17116/jnevro202112112157
115. Zastrozhin M, Skryabin V, Sorokin A, et al. Using a pharmacogenetic clinical decision support system to improve psychopharmacotherapy dosing in patients with affective disorders. Drug Metab Pers Ther. 2020;35(4). doi: 10.1515/dmpt-2019-0033
116. Zastrozhin MS, Sorokin AS, Agibalova TV, et al. [Using a personalized clinical decision support system for dosing in psychopharmacotherapy in patients with affective disorders based on the pharmacogenomic markers]. Narkologia. 2018;17(6):31–42. Russian. doi: 10.25557/1682-8313.2018.06.31-42
117. Zastrozhin MS, Skryabin VYu, Smirnov VYu, et al. Impact of the Omics-Based Biomarkers on the Fluvoxamine's Steady-State Concentration, Efficacy and Safety in Patients with Affective Disorders Comorbid with Alcohol Use Disorder. Psychopharmacol Bull. 2021;51(1):69–80.
118. Zastrozhin MS, Smirnov VV, Zastrozhina AK, et al. The estimation of influence of CYP3A activity on the efficacy and safety of fluvoxamine in patients with depressive disorders comorbid with alcohol use disorder. Journal of Siberian Medical Sciences. 2020;(1):65–75. doi: 10.31549/2542-1174-2020-1-65-75
119. Zastrozhin MS, Smirnov VV, Sorokin AS, et al. [Influence of CYP3A Activity on the Efficacy and Safety of Fluvoxamine in Patients Depressive Disorders and Comorbid Alcohol Use Disorder]. Vestnik Rossijskoj akademii medicinskih nauk. 2018;73(6):411–419. Russian. doi: 10.15690/vramn1035
120. Zastrozhin M, Skryabin V, Smirnov V, et al. Effect of Genetic Polymorphism of the CYP2D6 Gene on the Efficacy and Safety of Fluvoxamine in Major Depressive Disorder. Am J Ther. 2021;29(1):e26–e33. doi: 10.1097/MJT.0000000000001388
121. Zastrozhin M, Antonenko A, Grishina E, et al. [Evaluation of CYP2C19*3 effectiveness and safety of fluvoxamine in patients with depressive disorders, comorbide with alcoholism]. Psihiatrija, psihoterapija i klinicheskaja psihologija. 2018;9(4):578–589. Russian.
122. De Berardis D, Fornaro M, Serroni N, et al. Agomelatine beyond borders: current evidences of its efficacy in disorders other than major depression. Int J Mol Sci. 2015;16(1):1111–1130. doi: 10.3390/ijms16011111
123. Gorwood P, Benichou J, Moore N, et al. Agomelatine in Standard Medical Practice in Depressed Patients: Results of a 1-Year Multicentre Observational Study In France. Clin Drug Investig. 2020;40(11):1009–1020. doi: 10.1007/s40261-020-00957-9
124. Ter Meulen WG, Draisma S, van Hemert AM, et al. Depressive and anxiety disorders in concert-A synthesis of findings on comorbidity in the NESDA study. J Affect Disord. 2021;284:85–97. doi: 10.1016/j.jad.2021.02.004
125. Petelin DS, Niinoya IV, Sorokina OV, et al. [Treatment of mixed anxiety and depressive disorder: results from a observational study of the efficacy and tolerability of agomelatine]. Nevrologiya, neiropsikhiatriya, psikhosomatika. 2021;13(6):48–54. Russian. doi: 10.14412/2074-2711-2021-6-48-54
126. Gushanskaya EV, Frolova VI, Medvedev VE. [Therapy of anxious depression (experience with agomelatine)]. Psihiatrija i psihofarmakoterapija. 2015;17(1):17–21. Russian.
127. Butova VM. [The efficacy of Valdoxan in patients with chronic somatic diseases in relation to anxiety and depressive background and the quality of sleep]. Psihicheskie rasstrojstva v obshhej medicine. 2015;(4)40–42. Russian.
128. Avedisova AS, Zakharova KV, Marachev MP. [The results of observational studies JAZZ: remission, predictors of its formation and tolerability of Valdoxane (agomelatine) in patients with anxious depression within major depressive disorder]. Psihiatrija i psihofarmakoterapija. 2014;16(4):4–9. Russian.
129. Pribytkov AA, Panova NB, Popova YuV, et al. [Efficacy of agomelatine in depressive disorders with anxiety]. Zhurnal nevrologii i psihiatrii im. S.S. Korsakova. 2013;113(11 Pt 2):53–58. Russian.
130. Avedisova AS, Zaharova KV, Marychev MP. [The results of observational studies «JAZZ»: «The efficacy of agomelatine (Valdoxan) in the treatment of patients with anxious depression as part of a major depressive disorder»]. Psihiatrija i psihofarmakoterapija. 2013;15(6):14–22. Russian.
131. Dubnitskaya EB. [Experience of using fluvoxamine (fevarin) in psychogenic depression]. Psihiatriya i psihofarmakoterapiya. 2005;7(2):77–78. Russian.
132. Goodwin GM. Revisiting Treatment Options for Depressed Patients with Generalised Anxiety Disorder. Adv Ther. 2021;38(Suppl 2):61–68. doi: 10.1007/s12325-021-01861-0
133. Jiang J, Wu YJ, Yan CH, et al. Efficacy and safety of agomelatine in epilepsy patients with sleep and mood disorders: An observational, retrospective cohort study. Epilepsy Behav. 2024;152:109641. doi: 10.1016/j.yebeh.2024.109641
134. Fedorova NV, Kulua TK, Gubareva N. [Depression in Parkinson's disease. Efficacy of the new antidepressant drug Valdoxan (agomelatine) in correction of affective and dissomnic disorders]. Psihiatriya i psihofarmakoterapiya. 2015;17(4):9–14. Russian.
135. Avila A, Cardona X, Martin-Baranera M, et al. Agomelatine for Depression in Parkinson Disease: Additional Effect on Sleep and Motor Dysfunction. J Clin Psychopharmacol. 2015;35(6):719–723. doi: 10.1097/JCP.0000000000000404
136. Golubev VL, Pilipovich AA, Goytemirova PU. [Depression and sleep disturbances in patients with Parkinson's disease: role of Valdoxan in their correction]. Psihicheskie rasstrojstva v obshhej medicine. 2014;(1):51–55. Russian.
137. Gustov AV, Aleksandrova EA, Parshina EV, et al. [Optimization approach to therapy and psycho-emotional disorders and dyssomnia in Parkinson's disease]. Psihicheskie rasstrojstva v obshhej medicine. 2015;(2-3):54–58. Russian.
138. Marsh L, McDonald WM, Cummings J, et al. Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH Work Group. Mov Disord. 2006;21(2):148–58. doi: 10.1002/mds.20723

139. Rabey JM, Orlov E, Korczyn AD. Comparison of Fluvoxamine versus Amitriptyline for treatment of depression in Parkinson's disease. Neurology. 1996;46:A374.
140. Montgomery P, Yaffe J, Hopewell S, et al. Empty Reviews Project Group: [meeting report]. Running on Empty: The Cochrane Empty Reviews Project report of findings and consensus group feedback [Internet]. 2011 [cited 2024 Jul 12]. Available from: https:emptyreviews.files.wordpress.com
141. Gray R. Empty systematic reviews: Identifying gaps in knowledge or a waste of time and effort? Nurse Author & Editor. 2021;31(2):42–44. doi: 10.1111/nae2.23
142. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol. 2018;18(1):143. doi: 10.1186/s12874-018-0611-x