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ROLE OF MELATONIN IN THE MANAGEMENT OF SLEEP DISORDERS IN SCHIZOPHRENIA: A LITERATURE REVIEW

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ABSTRACT

Introduction and Objective: Sleep and circadian rhythm disturbances are highly prevalent in Schizophrenia and significantly impact symptom severity, disease progression, and treatment outcomes. Schizophrenia, a chronic and disabling mental illness affecting approximately 1% of the global population, is particularly associated with pronounced sleep abnormalities. Over 80% of patients with schizophrenia experience reduced sleep efficiency and delayed sleep onset. These disturbances are closely linked to worsening psychotic symptoms, cognitive dysfunction, and diminished quality of life. This review aims to explore the role of melatonin in these disruptions and its potential as an adjunctive treatment in Schizophrenia.
Materials and methods: Articles in PubMed, GoogleScholar, ScienceDirect databases were retrieved by the authors. The authors searched with keywords: melatonin, schizophrenia, sleep disorder, circadian rhythms, psychiatric disease. Articles between 2000 and 2024 were included.
Results: Randomized controlled trials show that prolonged-release melatonin (2–10 mg, 1–2 hours before bedtime) improves sleep latency, efficiency, and duration in schizophrenia. Melatonin, immediate-release, has variable findings; low doses (<1 mg) are used to treat circadian disorders, while higher doses (3–12 mg) are used to treat insomnia. Melatonin will also improve benzodiazepine withdrawal insomnia and help habituate to sleep in a novel environment. It is tolerable with mild but occasional side effects, but larger, high-quality trials are needed.
Conclusions: Melatonin is of great promise as an adjunct to sleep and circadian disturbance treatment in schizophrenia and related psychiatric illnesses, but more extensive research must be conducted to confirm its long-term safety and clinical efficacy.

KEYWORDS

Melatonin, Schizophrenia, Sleep Disorders, Circadian Rhythms, Psychiatric Illnesses

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1. Introduction

Schizophrenia is a chronic psychiatric disorder with a typical age of onset during adolescence or early adulthood. It is diagnosed by a constellation of positive symptoms, including delusions and hallucinations, and negative symptoms, e.g., affective flattening, social withdrawal, and cognitive impairment. Etiology involves dopaminergic dysregulation connected with immune-inflammatory activation, oxidative stress, and neurodevelopmental pathology, including brain structural abnormalities.

In schizophrenia, circadian rhythm disruption and sleep disturbance are of clinical importance, typically emerging before psychosis onset and persisting throughout illness. Significantly, the disturbances are frequently treatment refractory and negatively influence the clinical course, leading to enhanced symptom severity and poorer functional outcomes.

Sleep and circadian dysregulations are common features of psychiatric disorders that impact disease onset, course, and treatment response. To this purpose, melatonin—a neurohormone secreted by the pineal gland—has been a molecule of interest. Melatonin is an essential regulator of the circadian system and sleep–wake cycle with a circadian release pattern. [5][29].

Melatonin secretion is typically abnormal in schizophrenic patients, along with morphological abnormalities of the pineal gland like reduced volume and increased calcification. These changes have been associated with disturbed circadian rhythms and poor sleep quality, alongside cognitive impairment and deterioration of function. Despite the standard treatment of sleep disturbances in schizophrenia through routine sedating antipsychotic administration, these strategies rarely address the underlying circadian dysregulation and can yield significant metabolic side effects. Because of its biological role and tolerable safety profile, melatonin has also been studied more and more as an adjunct treatment of circadian and sleep disorders in

schizophrenia. Current controlled trials work has begun to investigate the potential therapeutic mechanism, speculating that treatment with exogenous melatonin could not only improve sleep regulation but also affect principal pathophysiological processes of the disease. [11][24].

2. Methodology

A structured search of the literature was conducted, restricted to publications between 2000 and 2024. The literature contained controlled trials, meta-analyses, systematic reviews, and clinical guidelines, and in particular clinical response rates, relative efficacy, side effect profiles, technical parameters, and the use of melatonin in combination with pharmacotherapy. The PubMed and Google Scholar databases were searched using the key term "melatonin," alone and with similar keywords such as "schizophrenia," "circadian disorders," and "pathophysiology of sleep." English language only publications were utilized. Ten researchers independently screened and chose applicable studies referred to in the search results.

1. The Significance of Sleep Disturbances in the Schizophrenia

Schizophrenia is a long-standing and debilitating mental disorder that affects about 1% of the global population. It is defined by a range of symptoms, both positive and negative. The positive symptoms include delusions, hallucinations, and disorganized thinking, whereas the negative symptoms consist of emotional blunting, poverty of content of speech, social withdrawal, and severe cognitive impairment [6][27]. Notwithstanding the lack of current official status in schizophrenia's diagnostic criteria, overwhelming data suggest they are extremely prevalent, occurring in more than 80% of schizophrenia patients [32]. Normal sleep disturbances in schizophrenia consist of decreased sleep efficiency, increased sleep onset latency, and disrupted sleep patterns [21]. These disruptions are significantly associated with worse clinical outcomes, such as heightened psychotic episodes, more symptoms of depression and anxiety, cognitive impairment, reduced quality of life, and an increased risk of suicidal behavior [12][26]. Insomnia and nightmares are two of the most common sleep disturbances found in this population and are reported to be present in over half of patients suffering from persecutory delusions [32]. Sleep-related problems have been recognized as a fundamental aspect of schizophrenia for more than a century, first documented by Kraepelin in 1919. These disturbances occur throughout all stages of the illness, including in individuals who experience early, prodromal symptoms. Similar issues have also been reported in first-degree relatives who do not have psychotic symptoms. Sleep disruptions often appear before the onset of psychosis and can serve as early warning signs for relapse. The presence of sleep problems in individuals who have never taken antipsychotic medication suggests that these disturbances are not merely side effects of treatment but may be a core feature of the disorder itself. Among the various sleep complaints, insomnia is the most commonly reported by people with schizophrenia. This includes difficulties with both falling asleep and staying asleep. Objective sleep studies using polysomnography, which records brain activity along with eye movements and muscle tone, often show that individuals with schizophrenia experience poorer sleep quality. Common findings include reduced sleep efficiency, longer time needed to fall asleep, and more frequent awakenings during the night. These studies also reveal abnormalities in sleep architecture, meaning the way time is distributed across different stages of sleep. Both patients who are taking antipsychotic medication and those who have never taken it, as well as their close relatives, frequently show disruptions in N3 sleep - including reduced duration and power of the large delta waves (~1–4 Hz) [15][14].This shorter duration and lower intensity of delta waves, which are important for deep sleep. Alterations in REM sleep have also been noted, such as reduced duration and delayed onset. While one meta-analysis has found consistent abnormalities in both N3 and REM sleep among individuals with schizophrenia, other studies have not observed clear or consistent differences when compared to healthy individuals or people with other psychiatric conditions [15][7].

3. Melatonin's Mechanism of Action

Melatonin acts by binding to melatonin receptors (MT1 and MT2) in the suprachiasmatic nucleus of the hypothalamus, thereby controlling the circadian clock [4][9][13]. Melatonin also has antioxidant properties and influences a number of neurotransmitter systems, which may be implicated in its therapeutic effects in psychiatric illness [1][23]. Melatonin plays a role in the control of sleep and circadian rhythms. Disorders of melatonin secretion and regulation have been found to occur in the majority of mental disorders. Such disorders may be caused by reduced secretion by the pineal gland or disruption of its release.

Exogenous melatonin is effective in treating certain sleep disorders and circadian rhythm disturbances. Its action on sleep and circadian timing is mediated primarily through melatonin receptors 1 (MT1) and 2 (MT2) [13]. MT1 receptor plays a part in resetting circadian rhythm timing and controlling REM sleep, whereas MT2 receptor is believed to control NREM sleep. However, it is not yet known whether the results can be generalized to all mentally disordered patients [9].

4. Impact of Antipsychotic Treatment on Melatonin Levels and Circadian Rhythm Disturbances in Schizophrenia

Melatonin has also been therapeutically helpful with its resynchronizing effect in circadian rhythm disturbances. Nevertheless, evidence has emerged that typical antipsychotic treatment would have an adverse impact on melatonin regulation in schizophrenic patients. In one recent study, the serum melatonin at 2:00 AM was well below normal physiological levels in both the groups treated with haloperidol and risperidone. Both at four weeks of treatment, serum and urinary melatonin concentrations decreased in both instances statistically—serum melatonin in the haloperidol-treated (2.42; 95% CI: 0.67–4.17; $p = 0.008$) and risperidone-treated (3.40; 95% CI: 0.54–6.25; $p = 0.021$) groups, and urinary melatonin in the haloperidol-treated group ($p = 0.005$) and the risperidone-treated group ($p = 0.014$) [13]. Furthermore, PSQI scores in both haloperidol ($p = 0.001$) and risperidone ($p = 0.003$) groups were significantly increased, demonstrating worsening in sleep quality. Despite symptom severity reduction, as measured by Positive and Negative Syndrome Scale (PANSS), in both the groups, baseline melatonin in serum levels correlated negatively with PANSS scores ($r = –0.5$), suggesting a reverse correlation between symptom burden and melatonin levels. In conclusion, monotherapy with risperidone and haloperidol can induce symptomatic remission in schizophrenia: they do not effectively treat and may worsen sleep and circadian rhythm disturbance. Due to the participation of melatonin in circadian regulation and claimed therapeutic action, adjunctive melatonin or melatonin receptor agonist could be a useful tactic to enhance sleep-impaired deficit in this population [13]. These findings are consistent with earlier studies that have reported a blunted nocturnal melatonin peak that persisted despite long-term neuroleptic treatment. In some studies, no significant melatonin secretion pattern alterations were noted following olanzapine treatment or between drug-free and medicated patients. These consistent findings suggest that typical antipsychotic medications are not able to restore, and even exacerbate, abnormalities in melatonin production [18].

5. Melatonin in Schizophrenia: Clinical Potential

There are various studies that have investigated the efficacy of melatonin in treating schizophrenia-related sleep disorders. A clinical trial systematic review indicates that melatonin supplementation improves sleep parameters, including sleep onset latency, sleep efficiency, and total sleep time, in schizophrenia patients [2][22]. Melatonin is also linked with improvements in tardive dyskinesia symptoms and with metabolic profile alterations in schizophrenia patients [28].

There is increasing evidence that the secretion of melatonin is often changed in schizophrenia patients, possibly due to calcification of the pineal gland and disrupted circadian control [19][30]. There have been genetic studies demonstrating specific variants within the MTNR1A melatonin receptor gene—most notably the rs2119882 polymorphism—to be associated with insomnia in schizophrenia patients. Besides, clinical observations consistently demonstrate that reduced melatonin levels correlate with greater sleep latency, diminished total sleep time, and diminished sleep efficiency, substantiating the phenomenon of circadian rhythm dysregulation in these subjects [11].

Due to the central role of melatonin in regulating the sleep–wake cycle, it has become a promising therapeutic target [11]. Clinical trials of ramelteon, an agonist of the selective melatonin receptors, show potential for cognitive enhancement, particularly in memory and learning domains, among schizophrenia patients [17]. These findings underscore the need for treating sleep disturbances in schizophrenia—both to improve sleep quality and to oppose more diffuse psychiatric symptoms and cognitive impairments [11][17]. Melatonin (N-acetyl-5-methoxytryptamine) exhibits antioxidant properties. Reduction of oxidative stress, elevation of brain-derived neurotrophic factor (BDNF), and regulation of dopaminergic systems by inhibiting the release of dopamine in the respective regions of the brain are its postulated mechanisms of action. Some limitations have been identified in the available evidence base: small numbers of participants, short trial durations (4–12 weeks), poor reporting of drug side effects and cognitive effect, and lack of dose-response analyses. Additionally, evidence on cognitive effects is derived from a single RCT and thus cannot be extrapolated to other environments. Despite these limitations, melatonin remains a promising, widely available, and well-tolerated candidate for adjunct therapy. Nonetheless, more extended follow-up periods and large-scale, high-quality studies are needed to ascertain its long-term tolerability and clinical utility [28].

6. Optimal Clinical Use of Melatonin Dosage and Timing

The dosage and timing of melatonin therapy differ according to the psychiatric disorder and the type of sleep disturbance. In schizophrenia, 2–10 mg prolonged-release melatonin, given 1–2 hours before sleep, is most often used to enhance sleep quality [22]. Immediate-release melatonin may be utilized in circadian rhythm disruption in doses typically less than 1 mg [20]. Evidence from randomized controlled trials (RCTs)

is growing for the therapeutic efficacy of melatonin in schizophrenia, particularly for the management of sleep symptoms. Prolonged-release (PR) melatonin, 2 mg, administered 1–2 hours before bedtime, has been found to have significant advantages in sleep efficiency, sleep onset latency, and total sleep duration. In accordance with current international practice guidelines for insomnia management, PR melatonin in doses of 2 mg, given 1–2 hours prior to bedtime, has been shown to be clinically effective at improving parameters of sleep in this group. Immediate-release (IR) melatonin in doses ranging from 3 to 12 mg has also been used, with outcomes remaining inconsistent, especially regarding subjective improvements in sleep. For circadian rhythm disorders like delayed sleep phase syndrome (DSPS), low-dose IR melatonin (≤ 1 mg) has been suggested worldwide, optimally taken 2–6 hours before bedtime. This may be particularly relevant in schizophrenia, in which circadian desynchronization is prevalent.

PR melatonin (2 mg) as a safe, effective, and potentially beneficial adjuvant strategy for insomnia treatment and benzodiazepine tapering in schizophrenia [22]. It can also be of clinical value during the discontinuation of sedative-hypnotic medications. Immediate-release (IR) melatonin, administered in doses ranging from 3 to 12 mg, has also shown some potential in the alleviation of subjective insomnia symptoms, although the evidence remains uncertain and requires further investigation [16][19]. New findings support the use of melatonin as an adjunctive therapy for insomnia associated with schizophrenia, particularly in the case of benzodiazepine withdrawal. A randomized controlled trial involving 76 patients found that administration of prolonged-release (PR) melatonin at a dose of 2 mg was effective in reducing the symptoms of insomnia in the context of benzodiazepine withdrawal, implicating its potential role in sleep continuity improvement during sedative-hypnotic discontinuation. PR melatonin may also be employed as an adjunctive therapy in the course of benzodiazepine withdrawal, alleviating insomnia symptoms that usually occur upon withdrawal [3][10]. Moreover, several studies suggest that melatonin is able to reduce the so-called "first-night effect" and thereby enhance sleep adaptation and alertness in novel sleeping environments [19][26][25].

Table 1. Melatonin Use in Various Sleep Disorders

Type of disorder	Melatonin formulation	Dose range	Time of administration	Reported benefits
Schizophrenia-related insomnia	Prolonged-release	2–10 mg	1–2 h before bedtime	↑ Sleep efficiency, ↓ latency
Circadian rhythm disorder	Immediate-release	0.3–1 mg	30–60 min before sleep	Restored circadian rhythm
Benzodiazepine withdrawal	Prolonged-release	2–3 mg	Bedtime	Reduced withdrawal insomnia
Cognitive dysfunction	Ramelteon	8 mg	Bedtime	↑ Memory, ↑ learning

7. Safety and Tolerability

7.1. General Safety and Tolerability

Systematic reviews of randomized, placebo-controlled trials currently describe melatonin as being well-tolerated by the general population with minimal adverse effects. The most common side effects compared to placebo were mild and included daytime sleepiness (~1.66%), headache (~0.74%), and dizziness (~0.74%). These trials generally employed dosages ranging from 0.15 mg to 15 mg daily and were relatively short-term in duration (<12 weeks), making definitive conclusions regarding long-term safety difficult [8][31].

7.2. Dose Considerations

To add evidence for these findings, post-marketing surveillance data also support the safety of melatonin, with minimal adverse event rates being reported—less than 10% in small-scale studies and as low as 0.008% in large populations. While dependence and withdrawal are rare, they have been reported on rare occasions, particularly in neurologically vulnerable groups. Importantly, side effects are not clearly dose-related, though doses in excess of 10 mg/day may increase the incidence of minor side effects such as headache and drowsiness without a corresponding increase in major risks. In view of the increasing use of higher doses, especially in research in neurodegenerative disorders, cautious surveillance is warranted [31].

7.3. Sedation and Cognitive Effects

The prime use of melatonin as a hypnotic agent raises questions regarding sedation and cognitive impairment. There is, however, evidence of restricted next-day sedation, particularly when melatonin is properly administered in the evening. While subjective sleepiness has been noted in several studies, these

effects do not necessarily translate to significant psychomotor impairment. Notably, rebound insomnia a common complication after discontinuation of benzodiazepines - has not been noted with melatonin withdrawal. In addition, systematic reviews have not established consistent psychiatric adverse effects, including depression, associated with melatonin use [31].

7.4. Cardiovascular Effects and Metabolic Effects

From the cardiovascular perspective, melatonin may have a mild antihypertensive effect, especially with long-release formulations. Although generally well tolerated, there have been some reports of palpitations, and the influence of melatonin on diurnal blood pressure variation would suggest that blood pressure monitoring should be contemplated, particularly in the elderly. Importantly, there has been no risk of elevated major cardiovascular events reported. For metabolic effects, melatonin has been found to worsen glucose tolerance and insulin sensitivity in certain groups, but when given nocturnally, the risk is seemingly small. One study in patients with type 2 diabetes found minimal adverse metabolic effects and even suggested that glycemic control may improve with time. Evidence concerning body weight is still unclear, with small amounts of weight loss being noted in young adults but no effect in elderly groups [31].

7.5. Clinical Considerations

Due to the broad systemic effects of melatonin, prescribers should exercise caution when initiating therapy in patients with comorbid liver disease or in conditions predisposing the patient to labile blood pressure or falls. Clinicians should be alert for adverse effects once treatment is initiated. Overall, melatonin carries low potential for severe adverse effects across different age groups, with mild side effects being most commonly reported. Additional research is warranted to establish the long-term safety profile of melatonin, particularly in older adults [8].

8. Limitations and Future Directions – Discussion

While there is recent evidence to support the efficacy of melatonin in treating sleep and circadian rhythm disorders of psychiatric illnesses, primarily schizophrenia, some limitations of the existing literature have to be highlighted. A major shortcoming of many studies is their limited sample sizes, brief follow-up duration, and nonuniform research strategies, and these diminish the generalizability and clinical applicability of their findings. To overcome these limitations, the future studies would be optimally designed large-scale multicenter clinical trials with more patients, especially schizophrenia patients. These trials are vital to establish optimal and safe dosing regimens, validate treatment efficacy, and elucidate an overall safety profile. Moreover, a better understanding of the neurobiological mode of action of melatonin's therapeutic advantage in psychiatric disorders is necessary. This knowledge will not only increase the effectiveness of clinical interventions but also make them safer and more accurate, ultimately resulting in better patient outcomes.

9. Conclusions

Studies show the treatment of sleep disorders and circadian rhythm in patients with schizophrenia treated with melatonin substitution has demonstrated improved sleep parameters compared to traditional pharmacotherapy. Melatonin's positive effects were observed on sleep parameters, such as shortened sleep latency, sleep efficiency, and overall quality. The results of the meta-analysis emphasize that the dosage and timing of melatonin administration are two key factors determining its therapeutic effect. The long-acting form of melatonin has been found to produce a large impact on the measure of sleep compared to the immediate-acting type in patients with cognitive disorders. The mainly affective patients are recommended to use low, rapid-acting dosages. Monotherapy with risperidone and haloperidol may lead to symptomatic remission in patients with schizophrenia; however, these treatments are often ineffective in addressing sleep and circadian rhythm disturbances and may potentially worsen them. Considering the role of melatonin in circadian regulation and its therapeutic potential, the addition of melatonin or melatonin receptor agonists could serve as an effective strategy to improve sleep-related impairments in this population. Melatonin will also improve benzodiazepine withdrawal insomnia and help habituate to sleep in a novel environment. At the same time, melatonin's tolerability and safety are very high due to its antioxidant properties, which increase brain-derived neurotrophic factor levels and reduce neurotoxicity. Current knowledge is not yet satisfactory, and further studies in larger patient groups are needed. In summary, melatonin in the treatment of schizophrenia shows promise as an effective therapy. However, treatment must consider the dosage and form of melatonin, which vary for specific patient groups depending on the predominant symptoms.

Author's contributions

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