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Treatment Options for Insomnia in Schizophrenia: A Systematic Review

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ABSTRACT

Background Insomnia is a common feature of schizophrenia. Although several studies have been published about the influence of certain drugs on schizophrenia patients' sleep, there are no well-grounded recommendations about insomnia treatment in this clinical setting. The present review aimed to identify relevant empirical evidence on available treatments of insomnia in patients with schizophrenia, assessing their safety and efficacy.

Methods This is a systematic review of clinical trials investigating the effect of treatments for insomnia in patients with a diagnosis of schizophrenia. Data were obtained from Medline/PubMed, Embase, PsycInfo, and the Cochrane Library. Risk of bias was assessed in individual studies for selection, performance, detection, attrition, and reporting bias.

Results Four studies met inclusion criteria; 2 using melatonin, 1 using paliperidone, and 1 with eszopiclone. All reported positive results: melatonin increased sleep efficiency and total duration of sleep; paliperidone decreased sleep latency onset and increased total sleep time and sleep efficiency; eszopiclone decreased insomnia severity index.

Conclusions Despite a very limited number of specific studies on this matter, all 4 studies have shown good benefit/risk ratios and reviewed options—melatonin, paliperidone, and eszopiclone—might represent valid options for residual insomnia in schizophrenia.

Introduction

Schizophrenia (SCZ) is one of the costliest brain diseases in the world given its health and socioeconomic costs; the lifetime risk of developing SCZ is 0.7 % and its prevalence around 0.5 % [1]. Insomnia is a common feature of SCZ: patients frequently claim poor sleep quality and significant sleep disruption [2]. Typical disruptions of sleep continuity in individuals with SCZ include an increase in both sleep onset latency and time awake after sleep onset, as well as a decrease in total sleep time and efficiency measures. Typical disturbances in sleep architecture include reductions in stage-2 sleep, slow wave sleep, rapid eye movement (REM) sleep, and latency to REM sleep onset [3, 4]. SCZ patients may also experience sleep-wake cycle reversal, where the major sleep period occurs during daytime, with wakefulness at night. More frequently, patients describe severe insomnia, particularly during relapses or when experiencing positive symptoms. It is not unusual for prolonged periods of total sleeplessness to accompany states of psychotic agitation, and it has actually been shown that severe insomnia is one of the prodromal signs of impending psychotic decompensation or relapse [5].

Antipsychotics (APs) reportedly ameliorate dyssomnias associated with SCZ, namely insomnia, but patients commonly complain of unresolved insomnia despite ongoing AP treatment [2]. Rates of residual insomnia in SCZ patients treated with APs range from 16 % to 30 %; it is often associated with inadequate hyperarousal and sleep-related movement disorders [6]. Possible side effects of APs—most frequently akathisia but also restless legs syndrome—are partly responsible [7].

Current SCZ treatment guidelines do not address residual insomnia in SCZ. In clinical practice, one of the following options is commonly chosen: (1) increasing the dose of the current AP; (2) switching to a sedative AP; (3) adding a low dose of a sedating AP;

or (4) using anxiolytics, hypnotics, or other non-AP sedative drugs as adjuvant therapy [2]. Any of these strategies is not without risks: switching from an otherwise efficacious AP drug to a more sedating but perhaps less efficacious compound might increase the risk of psychotic relapse. Adding another drug carries the disadvantages of polypharmacy, including increased side effects and drug-drug interactions, patient non-compliance, and medication errors.

Although some studies on pharmacological treatment options for sleep problems in patients with SCZ have been conducted, few interventions were robustly tested, as discussed by Baandrup et al. [8]. Our systematic review aimed to identify relevant empirical evidence on available treatments for insomnia in patients with SCZ, as well as their safety and efficacy.

Methods

Data sources and search strategy

Computerized Medline, Embase, PsycInfo, and Cochrane searches were performed using the terms "sleep" AND "schizophren*". Reference lists of retrieved studies were hand searched in order to identify any additional relevant studies. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed [9].

Inclusion and exclusion criteria

Original studies investigating pharmacological treatments for insomnia in patients with a diagnosis of SCZ as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were eligible for this systematic review if they met all of the following criteria: (i) publication date between January 1970 and July 2017, (ii) written in the English or Portuguese languages, (iii) publication in a peer-reviewed journal, (iv) comparison of subjective or objective measures of sleep between 2 groups (those treated with the study drug and those treated with no changes in the treatment), (v) patients aged 18 years or older. Studies were excluded if they (i) were single-case reports or review articles, (ii) reported duplicate data, (iii) studied a population with no insomnia, and (iv) related to animal studies.

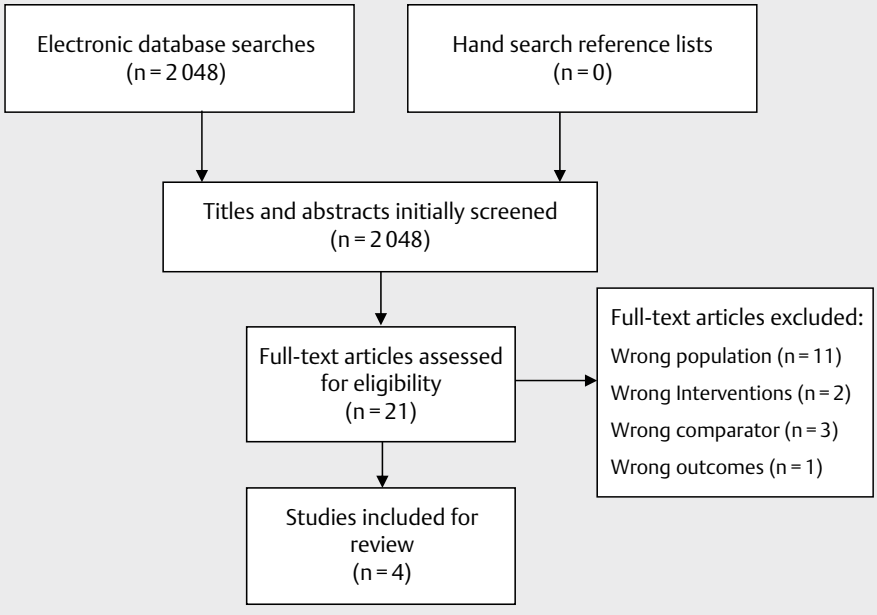
Data abstraction

After performing the initial literature searches, each study title and abstract was screened for eligibility by the first author. Full texts of all potentially relevant studies were retrieved and further examined for eligibility. The PRISMA flow diagram (▶ **Fig. 1**) provides detailed information. Once a study was included, data were extracted and entered into a normalized database that included (i) date of publication and country of recruitment, (ii) type of study, (iii) diagnostic criteria for SCZ and insomnia, (iv) number of subjects in each arm, (v) number of smokers, (vi) mean age, (vii) percentage of males, (viii) intervention protocol and endpoints used for assessment, (ix) statistically significant results, (x) adverse events, (xi) risk of bias in individual studies, and (xii) limitations. Risk of bias was determined using Cochrane Collaboration's tool [10]; the following biases were analyzed: (i) selection, (ii) performance, (iii) detection, (iv) attrition, and (v) reporting bias. Quality of studies was scored using the Jadad Scale [11].

Results

Four articles were included in this review: 2 studying melatonin [12, 13], 1 studying paliperidone [14], and 1 studying eszopiclone [15].

Studies were from Israel, India, and United States, and a fourth study had a multicentric design involving 8 European centers (Poland, France, and Romania). Reviewed studies included a total of 129 participants: 76 were allocated to an active treatment arm.



▶ **Fig. 1** PRISMA flow diagram of the study selection process.

▶ **Table 1** Treatment options for residual insomnia in schizophrenia.

Reference	Inclusion criteria	Treatment	Type of study	Measures evaluated	Statistically significant results	Adverse events
Shamir et al., 2000	Schizophrenia (DSM-IV) Insomnia (DSM-IV)	2 mg of XR melatonin	RCT	Actigraphy	↑ Sleep efficiency (in global population) ↑ Sleep efficiency (in poorer sleepers)	No information
Kumar et al., 2007	Paranoid schizophrenia (DSM-IV) Initial insomnia (latency sleep onset < 30 min)	3–12 mg of melatonin	RCT	Questionnaire (latency sleep onset, number of awakenings, and duration of sleep)	↓ Nighttime awakenings ↑ Duration of sleep	Fewer morning headaches with melatonin No significant differences in Drowsiness after taking the medication Oniric activity Heaviness of head on awakening Experience of freshness during the day
Luthringer et al., 2007	Schizophrenia (DSM-IV) Insomnia (sleep efficiency index < 85 %)	9 mg of XR paliperidone	Multicentric RCT	PSG, LSEQ, PANSS, and CGI-S	↓ Latency sleep onset and nighttime awakenings ↑ Total sleep time and sleep efficiency ↓ Stage 1 NREM ↑ Stage 2 NREM and REM	Mild to moderate forms of Dystonia Extrapiramidal disorder Headache Oculogyric crisis
Tek et al., 2014	Schizophrenia or schizoaffective disorder (DSM-IV) Insomnia severity index ≥ 10	3 mg of eszopiclone	RCT	ISI score, PANSS, Q-LES-Q-18, CDS, MATRICS, SAFTEE-SI, and a questionnaire about sleep diary items	↓ ISI score Improvement of concentration problems and "general feeling upon rising"	Mild forms of Unpleasant taste Sedation Headache Dry mouth

RCT: randomized controlled trial; PSG: polysomnography; LSEQ: Leeds Sleep Evaluation Questionnaire; NREM: non-rapid eye movement; ISI: Insomnia Severity Index; L-LES-Q-18: Quality of Life Enjoyment and Satisfaction Questionnaire; MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia; SAFTEE-SI: Systematic Assessment for Treatment Emergent Events-Systematic Inquiry.

▶ **Table 2** Assessment of risk of bias in individual studies and Jadad Score (0–5).

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Jadad Score
Shamir et al., 2000	+	−	−	?	?	4
Kumar et al., 2007	+	+	−	?	−	4
Luthringer et al., 2007	−	−	?	−	−	5
Tek et al., 2014	?	−	+	−	−	5

(+) high risk of bias; (−) low risk of bias; (?) unclear risk of bias.

The overall study population was skewed toward male participants (62.8 %); the median age of included subjects was 39.28 years. A summary of the results is presented on ▶ **Table 1** and the risk of bias in individual studies, based on the Cochrane Collaboration's tool and Jadad Score, is shown on ▶ **Table 2**.

In Shamir et al. [12], 19 patients with SCZ who were treated with the normal treatment regimen were given melatonin (2 mg, controlled release) or placebo for 2 treatment periods of 3 weeks each with 1 week washout between treatment periods (7 weeks total). Actigraphy was performed for 3 consecutive nights at the end of each period. Melatonin replacement significantly improved rest-derived sleep efficiency compared with placebo. Improvement of sleep efficiency was significantly greater in low-efficiency than high-efficiency sleepers.

In Kumar et al. [13], stable schizophrenic outpatients (n = 40) with initial insomnia of at least 2 weeks duration were randomly assigned to augment their current medications with either flexibly dosed melatonin (3–12 mg/night; n = 20) or placebo (n = 20). By use of a questionnaire, double-blind assessments of aspects of sleep functioning were obtained daily across the next 15 days. Relative to placebo, melatonin significantly improved the quality and depth of nighttime sleep without producing hangover.

In Luthringer et al. [14], patients received paliperidone extended-release 9 mg/day or matching placebo during the 14-day double-blind phase. Sleep architecture and sleep continuity were evaluated using polysomnograms. Subjective sleep measures were evaluated daily using the Leeds Sleep Evaluation Questionnaire. Efficacy and safety were also assessed. Thirty-six patients (17 on paliperidone extended-release, 19 on placebo) completed the study. Paliperidone extended-release treatment versus placebo resulted in clinically and statistically significant differences in sleep measurements from baseline to endpoint including a reduction in persistent sleep latency

(41 min), sleep onset latency (35 min), number of awakenings after sleep onset (7), time awake in bed (50 min), and stage 1 sleep duration (12 min); prolongation in total sleep time (53 min), sleep period time (42 min), stage 2 sleep duration (51 min), and REM sleep duration (18 min); and an increase in sleep efficiency index (11 %).

Tek et al. [15] was an 8-week randomized, double-blind, placebo-controlled clinical trial. Thirty-nine clinically stable outpatients with SCZ or schizoaffective disorder (symptomatically stable for at least 2 months prior to the study with a stable dose of AP medication for at least 1 month) and insomnia were randomized to either 3 mg eszopiclone (n = 20) or placebo (n = 19). The eszopiclone group received 2 mg every night before bedtime for the first week for evaluation of somnolence and 3 mg from week 2 to week 8. Primary outcome measure was change in Insomnia Severity Index (ISI) over 8 weeks. Total ISI scores decreased more in the eszopiclone group than in the placebo group.

Discussion

Our review aimed to assess empirical evidence on available pharmacological treatments for insomnia in patients with SCZ, regarding their safety and efficacy. Regarding the 4 treatment options initially described for residual insomnia in patients with SCZ (increasing the dose of the current AP; switching to a sedative AP; adding a low dose of a sedating AP; and using anxiolytics, hypnotics, or other non-AP sedative drugs as adjuvant therapy), only 2 were studied: AP switching (paliperidone [14]) and adjunctive use of an anxiolytic/hypnotic (melatonin [12, 13] and eszopiclone [15]).

Despite substantial methodological differences, both studies on melatonin demonstrated clear benefit in several sleep parameters. One study [12] described better outcomes in patients with more serious sleep disturbance, hypothesizing that sleep could not be improved beyond a certain ceiling. Only 1 study [13] evaluated melatonin's side effects, reporting no relevant symptoms; in fact, many parameters related to morning effects were associated with better outcomes than placebo; such benefits probably derived from better nighttime sleep. Shamir et al. used a fixed dose of modified-release melatonin with an objective evaluation method: actigraphy. Kumar et al. administered immediate-release melatonin as needed and used subjective evaluation methods. This study was the only one that used early insomnia as screening criteria; all remaining studies used less restrictive screening criteria, including patients with intermediate and terminal insomnia.

Melatonin is an endogenous sleep promoter secreted by the pineal gland with a diurnal variation, reaching peak levels at night [16]. The nighttime melatonin secretion peak is blunted in drug-free schizophrenic individuals and such a pattern seems to persist even after clinical improvement with APs; low melatonin might represent a major cause of insomnia in SCZ patients [17].

Eszopiclone is a pyrrolopyrazine derivative of the cyclopyrrolone class; its actions produce not only sedative-hypnotic but also anticonvulsant and tranquilizing effects [18]. The single study using eszopiclone [15] reported that it was an effective insomnia treatment option in SCZ patients, without significant adverse effects, the most common adverse effect being unpleasant taste. Unlike other studies, Tek et al. included patients with schizoaffective disorder. Although they did not use objective methods to evaluate sleep, SCZ symptomatology was assessed (Positive and Negative Syndrome Scale [PANSS] instrument); eszopiclone, although effective in insomnia treatment, had no impact on SCZ remaining symptomatology. Eszopiclone significantly increased sleep spindles. Some studies suggest that the spindle deficit in SCZ impairs sleep-dependent memory consolidation and may be ameliorated by eszopiclone [19].

Paliperidone is an atypical AP, a benzisoxazole derivative, and the principal active metabolite of risperidone [20]. The study that assessed paliperidone [14] was the only one that evaluated AP switching. The authors reported improvement in objective measures like sleep continuity and architecture but did not describe any correlation with clinical measures such as PANSS and Clinical Global Impression-Scale Severity (CGI-S). No statistically significant difference was found regarding patients' evaluations of their sleep. The most commonly reported adverse effects included headache, dystonia, oculogyric crises, and other extrapyramidal symptoms; most of the events were mild to moderate in severity. This study used a fixed dose (9 mg) of modified-release paliperidone. It was the only multicenter study reviewed, using both objective (polysomnography) and subjective (validated questionnaires) evaluation methods for insomnia evaluation.

Despite the importance of this concern, we only found 4 studies evaluating treatments for residual insomnia in people with SCZ. All studies were randomized controlled trials involving small populations. A major limitation on all articles was the short-term trials of treatment reported (2–8 weeks). Future studies are needed to investigate the long-term effects of selected drugs, as insomnia in SCZ is mostly chronic. Risk of bias, as shown in ▶ **Table 2**, was relatively small. The articles' lack of information regarding the selection of individuals for the control and testing groups made this the main issue regarding bias assessment. Although adding a low-dose sedative AP is commonly used as an off-label option, no article explored this possibility.

In conclusion, the evidence base is too scarce to extract robust clinical recommendations regarding the treatment of residual insomnia in SCZ. Despite the limited number of specific studies, all articles have shown good benefit/risk ratios, and the reviewed options—melatonin, eszopiclone, and paliperidone—might represent valid options for residual insomnia in SCZ. Further research is needed to improve our knowledge on a frequent challenge in patients with SCZ.

Conflicts of Interest

NM has served as a consultant or advisory board member for AstraZeneca, Ferrer and Janssen. All other authors report no conflicts of interest.

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