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The impact of eszopiclone on sleep and cognition in patients with schizophrenia and insomnia: A double-blind, randomized, placebo-controlled trial

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Abstract

Background—Insomnia is frequent in schizophrenia and may contribute to cognitive impairment as well as overuse of weight inducing sedative antipsychotics. We investigated the effects of eszopiclone on sleep and cognition for patients with schizophrenia-related insomnia in a double-blind placebo controlled study, followed by a two-week, single-blind placebo phase.

Methods—Thirty-nine clinically stable outpatients with schizophrenia or schizoaffective disorder and insomnia were randomized to either 3 mg eszopiclone ($n = 20$) or placebo ($n = 19$). Primary outcome measure was change in Insomnia Severity Index (ISI) over 8 weeks. Secondary outcome measure was change in MATRICS Consensus Cognitive Battery (MATRICS). Sleep diaries, psychiatric symptoms, and quality of life were also monitored.

Results—ISI significantly improved more in eszopiclone (mean = −10.7, 95% CI = −13.2; −8.2) than in placebo (mean = −6.9, 95% CI = − 9.5; −4.3) with a between-group difference of − 3.8 (95% CI = − 7.5; − 0.2). MATRICS score change did not differ between groups. On further analysis there was a significant improvement in the working memory test, letter–number span component of MATRICS (mean = 9.8 ± 9.2, $z = -2.00$, $p = 0.045$) only for subjects with schizophrenia on eszopiclone. There were improvements in sleep diary items in both groups with no between-group differences. Psychiatric symptoms remained stable. Discontinuation rates were similar. Sleep remained improved during single-blind placebo phase after eszopiclone was stopped, but the working memory improvement in patients with schizophrenia was not durable.

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Contributors

C. designed the present study. S.G. and C. undertook the statistical analysis. All authors contributed to the writing of the article. All authors have approved the final article.

Conflicts of interest

Drs. Palmese, DeGeorge, and Guloksuz report no financial relationships with commercial interests. Ms. Reutenauer reports no financial relationships with commercial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.10.002.

Conclusions—Eszopiclone stands as a safe and effective alternative for the treatment of insomnia in patients with schizophrenia. Its effects on cognition require further study.

Keywords

Schizophrenia; Insomnia; Sleep; Eszopiclone; Working memory; Cognition

1. Introduction

Sleep disturbances are common in schizophrenia; about half the patients suffer from poor sleep (Chouinard et al., 2004; Palmese et al., 2011). Insomnia associated with schizophrenia is present in all phases of the illness: prodrome, First episode, acute episode, and as a residual symptom in clinically stable patients (Lauer et al., 1997; Poulin et al., 2003; Keshavan et al., 2004). Despite the common occurrence of the problem, sleep in schizophrenia is not well studied (Krystal et al., 2008). Existing studies report decreased sleep efficiency, shortened REM latency, and decreased stage-4 sleep (Monti and Monti, 2005). Sleep problems have been shown to correlate with the severity of negative symptoms (Kato et al., 1999), contribute to lower subjective quality of life (Ritsner et al., 2004; Hofstetter et al., 2005), to be a moderate but significant predictor for relapse (Chemerinski et al., 2002) and lower psychosocial function in the long term (Goldman et al., 1996).

The lack of treatment studies addressing insomnia in schizophrenia presents two distinct problems. First, impaired cognition is a cardinal feature of schizophrenia, that is highly associated with outcome (Sheffield et al., 2014). Insomnia is associated with negative cognitive effects both in general population and schizophrenia (Goder et al., 2004; Manoach et al., 2004; Shekleton et al., 2010). Therefore, improving sleep may actually improve cognitive impairment in schizophrenia. Second, management of sleep-related problems in clinically stable schizophrenia patients is mostly based on clinician's personal preference. Clinicians usually shy away from hypnotics with abuse/dependence potential in this addiction prone population. Recent studies demonstrate the increasing use of antipsychotics with sedating properties for insomnia treatment (Ziedonis et al., 2005; Hermes et al., 2013). This treatment strategy involves either switching the current antipsychotic with a more sedating antipsychotic, or adding second antipsychotic to treatment. Unfortunately, these strategies bring along several problems: 1. switching the established antipsychotic carries the potential risk of relapse (Buckley and Correll, 2008); 2. sedating antipsychotics have all been associated with weight gain and metabolic syndrome (Leucht et al., 2013); and 3. polypharmacy increases side effects (Carnahan et al., 2006; Misawa et al., 2011).

Hypnotics with less abuse potential such as zolpidem and eszopiclone have not been well studied in schizophrenia. There are two small studies by a Japanese group who investigated zopiclone (Kajimura et al., 1994, 1995) reporting zopiclone to be superior to benzodiazepine hypnotics in terms of polysomnographic and subjective measures of sleep in schizophrenia. Surprisingly, zopiclone, but not benzodiazepine hypnotics, also induced modest improvements in negative symptoms. More recently, a two-night randomized placebo-controlled study of 21 patients with schizophrenia showed that eszopiclone use increased the

number and density of sleep spindles significantly more than placebo, but did not significantly enhance sleep dependent learning (Wamsley et al., 2013).

Identifying alternatives for treating corollary problems in schizophrenia is important for preventing the overuse of weight-promoting sedative antipsychotics, especially in the face of the current obesity epidemic and early mortality in schizophrenia. If cognition improves with improved sleep that would be an important added benefit. Eszopiclone has been shown to be an effective agent in primary insomnia and insomnia with psychiatric comorbidity (Krystal et al., 2012), and it does not have known metabolic side effects. Thus, we have conducted the current study to investigate the effects of eszopiclone on sleep and cognition as an add-on treatment for insomnia in patients with schizophrenia and schizoaffective disorder.

2. Method

2.1. Setting and participants

The study was conducted at a large community mental health center. This was an 8-week randomized, double-blind, placebo-controlled clinical trial of eszopiclone 3 mg for the treatment of schizophrenia-related insomnia. We added a two-week single-blind placebo phase to examine the durability of any improvement. Inclusion criteria were as follows: age between 18 and 64 years, English speaking, DSM-IV diagnosis of schizophrenia or schizoaffective disorder based on SCID interview, self-reported sleep difficulties at least twice per week in the preceding month, and an Insomnia Severity Index (ISI) rating ≥ 10. Participants were symptomatically stable for at least 2 months prior to the study with a stable dose of antipsychotic medication for at least 1 month, and no changes in antipsychotic type within the last 2 months. Exclusion criteria were as follows: alcohol or other substance dependence, dementia, mental retardation or other neurological disorders, sensitivity to eszopiclone, medical disorders likely to impair sleep like sleep apnea, pregnancy, clinically significant hepatic impairment, use of any medication that affects sleep/wake function (other than antipsychotic medications), and the use of potent cytochrome p450 3A4 inhibitor medications. Written informed consent was obtained from all participants. Study protocol was approved by IRB (Yale HIC#0702002331), and registered on ClinicalTrials.gov (NCT00645944).

2.2. Study design

Following a screening and baseline assessment, eligible patients were randomly assigned to either placebo or eszopiclone in a 1:1 ratio using a computer randomization procedure at the research pharmacy. The active and placebo medications were physically identical. 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. A two-week, single-blind placebo phase followed the double-blind phase. During the study period, no additional intervention to promote sleep hygiene was administered.

Patients were assessed weekly. The primary outcome measure was between-group change in ISI scores across the double-blind phase. The ISI is a 7-item self-report questionnaire that

provides a global measure of insomnia severity based on several indicators (e.g., difficulty falling or staying asleep, satisfaction with sleep, degree of impairment with daytime functioning). It has adequate internal consistency (Cronbach's $\alpha = 0.91$) and temporal stability ($r = 0.80$), has been validated against sleep diary and polysomnography data (Bastien et al., 2001), and was sensitive to change in previous studies (Morin et al., 1999). Additionally, patients were asked to complete a sleep diary to record sleep parameters each day. Sleep interviews assessing the sleep diary items were conducted through use of study-provided cellular phones each morning for the First 2 weeks and the last week of double-blind phase. Sleep diary items consisted of total sleep time (TST), wake after sleep onset (WASO), sleep latency, number of awakenings, daytime alertness, ability to concentrate, physical well-being, and ability to function on an 11-point Likert scale. Patients were also assessed every other week with the Positive and Negative Syndrome Scale (PANSS) and the Quality of Life Enjoyment and Satisfaction Questionnaire—Abbreviated Version (Q-LES-Q-18) to determine clinical symptom severity and quality of life, respectively. Calgary Depression Scale (CDS) scores were determined at baseline, week 4, 8 and 10. MCCB MATRICS Consensus Cognitive Battery (MATRICS) was used at baseline, week 8 and 10 to assess the following cognitive domains: processing speed, attention, verbal and nonverbal working memory, verbal and visual learning, reasoning/problem solving, and social cognition. A modified version of the Systematic Assessment for Treatment Emergent Events-Systematic Inquiry (SAFTEE-SI) was used to evaluate adverse events on a weekly basis. Urine drug toxicology and hcg pregnancy tests were performed at baseline, week 4 and 8, with positive findings resulting in exclusion from the study.

2.3. Statistics

Data were analyzed with the Stata computer program, version 12 (Stata Corporation, College Station, TX, USA). Data were analyzed according to modified intention-to-treat (ITT) principle, which included all randomized patients who received at least one dose of study medication and had at least one post-baseline measurement (Sainani, 2010). Baseline differences between groups were analyzed using Student *t*, Mann–Whitney, and chi-square tests for parametric, nonparametric, and categorical data, respectively. We have conducted a mixed model analysis utilizing XTMIXED routine in STATA software package. Our test for efficacy was the fixed effect for the drug group-by-study visit interaction, which, if significant, indicated that the change in outcome scores over time was significantly different among treatment groups. To allow for flexible trends over time, the time variable in the model was coded as a factor from baseline to week 8 and baseline served as the reference category. All models included fixed effects for treatment, study week, and the treatment-by-study visit interaction; least squares means at week 8 were the a priori basis for the treatment comparisons in the double-blind phase. The change from week 8 to week 10 in treatment groups during the single-blind phase was compared by Mann–Whitney test as the data did not meet assumptions of parametric tests. Time to treatment discontinuation in treatment groups was compared using log-rank test. Adverse event rates in treatment groups were compared using Fisher's exact test. MATRICS raw scores were translated into standardized *T*-scores, which were adjusted for age and gender. Differences between the treatment and placebo groups were determined using Mann–Whitney test for cognitive domains, which were assessed at baseline and week 8. Additional exploratory analyses were performed to

look separately at patients with schizophrenia and schizoaffective disorder. Two-sided statistical significance was set at $p < 0.05$.

3. Results

3.1. Disposition and baseline characteristics

A total of 179 outpatients were screened, 44 met initial eligibility criteria. Forty-three consented to participate in the study, and of these 4 were withdrawn prior to randomization (1 no longer interested, 2 tested positive for drug use, 1 hospitalized). Of the remaining 39, 19 were randomized to placebo, and 20 to eszopiclone 3 mg. Two participants in the placebo arm and 1 participant in the eszopiclone arm withdrew before receiving study medication (Supplementary Figure S1). Therefore, 36 participants were included in the modified ITT analysis. There were no differences between the groups in baseline demographic and clinical characteristics except PANSS general, and general feeling upon rising (Table 1).

3.2. Primary and secondary sleep outcome measures

Total ISI scores (the primary outcome) decreased more in the eszopiclone group (mean = − 10.7, 95% CI = −13.2; −8.2) than in the placebo group (mean = −6.9, 95% CI = − 9.5; −4.3) across the double-blind phase from baseline to week 8 (Table 2). After excluding the degree of impairment with daytime functioning item of the ISI, the difference in change in total ISI scores (composed of directly sleep related ISI items) between groups still remained significant with a between-group difference of − 3.4 (95% CI = − 6.7; − 0.2, $p = 0.038$). Fig. 1 shows the time course of ISI total scores predicted from the mixed multilevel model. Participants who received eszopiclone reported more improvement in both general feeling upon rising and concentration problems from baseline to week 8 (Table 2). Over 8 weeks, there were improvements in sleep diary items in both placebo, and eszopiclone groups with no significant difference between the groups (Table 2).

3.3. Clinical and cognitive measures

Changes in clinical measurements, and total QLES-Q-18 scores did not differ between the groups (Table 2). There was no difference in any of the cognitive domains between groups at baseline. Across the double-blind phase, there was no difference between placebo and eszopiclone groups in any of the cognitive domains tested, including the overall cognitive score (Table 3). In additional exploratory analyses there was trend level improvement in the overall cognitive score in schizophrenia (but not schizoaffective) patients on the eszopiclone (but not placebo) arm ($n = 6$, $z = -1.78$, $p = 0.075$). Additional analysis showed that this change is driven by a significant improvement of working memory test, letter–number span test scores ($z = -2.00$, $p = 0.045$) (Supplementary Figure S2). This improvement was correlated with the change of ISI score ($r = 0.84$, $p = 0.034$).

3.4. Single-blind placebo phase

There were no differences between placebo and eszopiclone groups in changes in total ISI score, and additional items assessing influence of sleep on functioning during the single-blind phase (Supplementary Table S1). Of the sleep diary items, only total number of awakenings increased slightly in the eszopiclone group (0.4 ± 0.8) compared to the placebo

group (−0.3 ± 0.5) (Supplementary Table S1). There was no evidence of worsening in either clinical measures or total QLES-Q-18 scores during the single-blind phase (Supplementary Table S1). The cognitive scores at single-blind phase end were not significantly different for either group from baseline, or from double-blind phase end. In additional analyses the significant improvement in working memory observed in schizophrenia patients on the eszopiclone arm during double-blind phase did not exist anymore (Table 3, and Supplementary Figure S2).

3.5. Tolerability and safety

Of the total sample, 9 (25%) patients did not complete the study and survival analysis indicated that the rates of discontinuation between groups did not differ ($p = 0.39$). In the placebo group, 1 patient withdrew voluntarily, 1 due to adverse event (unpleasant/metallic taste), and 1 due to protocol violation (substance use/treatment). In the eszopiclone group, 1 patient withdrew voluntarily, 2 due to adverse event (sedation and anxiety), 2 due to protocol violation (substance use/treatment), and 1 patient was lost to follow-up (Supplementary Figure S1). There was no difference between treatment groups in number of participants with at least 1 adverse event reported (13 (76.5%) placebo vs. 16 (84.2%) in eszopiclone groups, $p = 0.684$) (Supplementary Table S2). The adverse events were mild and most commonly included unpleasant taste, sedation, dry mouth and headache.

4. Discussion

To our knowledge, this is the First double-blind randomized controlled clinical trial investigating eszopiclone for the treatment of insomnia associated with schizophrenia. This study shows that add-on eszopiclone treatment over 8 weeks was associated with significantly more improvement than placebo in insomnia in patients with schizophrenia or schizoaffective disorder. Eszopiclone appeared to be a safe treatment, which was not associated with significant adverse effects, as most common adverse effect being unpleasant taste. Furthermore, there was no evidence for tolerance occurring to therapeutic effects of eszopiclone; and the improvement in sleep continued during the two-week single-blind placebo phase.

Sleep disturbances are common in schizophrenia, and are associated with reduced quality of life and cognitive functioning (Chouinard et al., 2004; Ritsner et al., 2004; Hofstetter et al., 2005). Additionally, insomnia in schizophrenia appears to predict psychotic exacerbation (Chemerinski et al., 2002). There are no treatment guidelines addressing residual insomnia in schizophrenia; and in clinical practice, antipsychotics with sedating properties, i.e, quetiapine, olanzapine are commonly utilized. These antipsychotics may be effective for insomnia initially; however, metabolic disturbances and weight gain paradoxically result in sleep problems associated with obstructive sleep apnea/hypopnea over time (Winkelman, 2001; Wirshing et al., 2002). In accordance with the studies in patients with primary insomnia, anxiety and depressive disorders (Krystal et al., 2007, 2012; Pollack et al., 2008; Ancoli-Israel et al., 2010), this study demonstrated that eszopiclone is an effective insomnia treatment option in patients with schizophrenia. Self-reported “general feeling upon rising” and “concentration problems” also improved more in the eszopiclone group than in the

placebo group. While all sleep diary items (i.e. sleep latency, TST, WASO, and number of awakenings) were improved in both groups over time, the difference between treatment groups was not statistically significant. Participants did not receive any formal behavioral intervention focused on insomnia; however, keeping a sleep diary, and weekly assessments both in person and via telephone might have served to regulate the sleep patterns of participants, thereby leading to a high placebo response (McCall et al., 2005).

Our findings showed no development of tolerance during the treatment phase during the discontinuation phase, in accordance with previous studies (Pollack et al., 2008; Ancoli-Israel et al., 2010; Uchimura et al., 2012). Moreover, long-term studies up to a year also support that eszopiclone can be safely used to treat primary insomnia with no tolerance and dependence issues (Roth et al., 2005; Walsh et al., 2007; Uchimura et al., 2012). Consistent with previous studies, adverse event rates were comparable to placebo (Pollack et al., 2008; Ancoli-Israel et al., 2010; Uchimura et al., 2012). The rates of daytime sedation were comparable to placebo as well. The patients remained clinically stable without any worsening in psychotic symptoms. Indeed, eszopiclone improved PANSS scores, though not statistically different than placebo. Quality of life did not improve in the study, but it is plausible that significant improvement in quality of life requires more than 8 weeks.

A recent study argues that two nights use of eszopiclone may improve sleep dependent memory consolidation by increasing sleep spindles, thus representing a potential treatment for cognitive impairment (Wamsley et al., 2013). We failed to demonstrate improvement in cognitive functioning. One possible explanation for the lack of cognitive improvement might be the relatively brief study duration. However, further analyses showed a significant working memory improvement in schizophrenia patients on eszopiclone, but not in the rest of the patients. This improvement did not survive the two-week placebo phase, but was correlated with improvement of sleep. The present study did not involve sleep encephalograms; therefore we cannot speculate on sleep spindle effects. The fact that working memory improvement disappeared after two-week single-blind placebo administration may indicate an actual acute effect of eszopiclone on working memory. Eszopiclone is an agonist on GABA-A receptors; and specific GABA-A modulators have previously been shown to improve working memory in schizophrenia (Lewis et al., 2008). A lack of similar effect in schizoaffective subjects is intriguing. This area clearly requires further research with adequate sample size and electrophysiological measures.

Although, we planned to reach a sample size of 80 outpatients in order to reach sufficient power for analyses of sleep diary and cognitive domains, we were able to recruit only 43 participants. The strict definition of clinical stability as inclusion criteria, and additional exclusion of patients with alcohol/substance abuse limited the sample size. Fortunately, the dropout rate was lower than typically observed in schizophrenia clinical trials. Moreover, multilevel mixed effect models enable more efficient data analysis by allowing the inclusion of all data from participants with missing data. However, the study remained underpowered when cognition was analyzed separately in schizophrenia and schizoaffective subjects. Actimeters were not financially feasible at the time of the study. Therefore, our findings are limited to subjective reports of sleep. Although, the ISI has been shown to be both valid and reliable in reflecting the sleep abnormalities measured with polysomnography (Bastien et al.,

2001), the validity of self-report measures has been questioned (Carskadon et al., 1976; Silva et al., 2007). To our knowledge, no self-report insomnia scale has been validated with the "gold-standard" polysomnography in schizophrenia thus far. However, one study showed that self-reported sleep measures in schizophrenia appeared to correlate well with actimeter measures in a small sample (Hamera et al., 2013). Future studies still should incorporate the use of actimeters, which are now more affordable. In terms of self-report measures, we went further than many insomnia trials by distributing cell phones to participants and calling them daily for morning sleep interviews to increase the reliability of self-reported sleep diary data.

Notwithstanding its limitations, findings of this study provide evidence for the effectiveness of add-on eszopiclone for insomnia treatment in schizophrenia. The potential advantage of eszopiclone over the sedating antipsychotics is its low impact on weight. Although long-term studies up to a year show eszopiclone is a safe medication for primary insomnia without evidence of tolerance and dependence, future studies should aim to investigate the long-term effects of eszopiclone, given that insomnia in schizophrenia is mostly chronic. Perhaps with longer-term treatment, functioning and cognition may improve. The study also provides, albeit a weak, signal for possible improvement of working memory in schizophrenia with a GABA-A agonist that requires further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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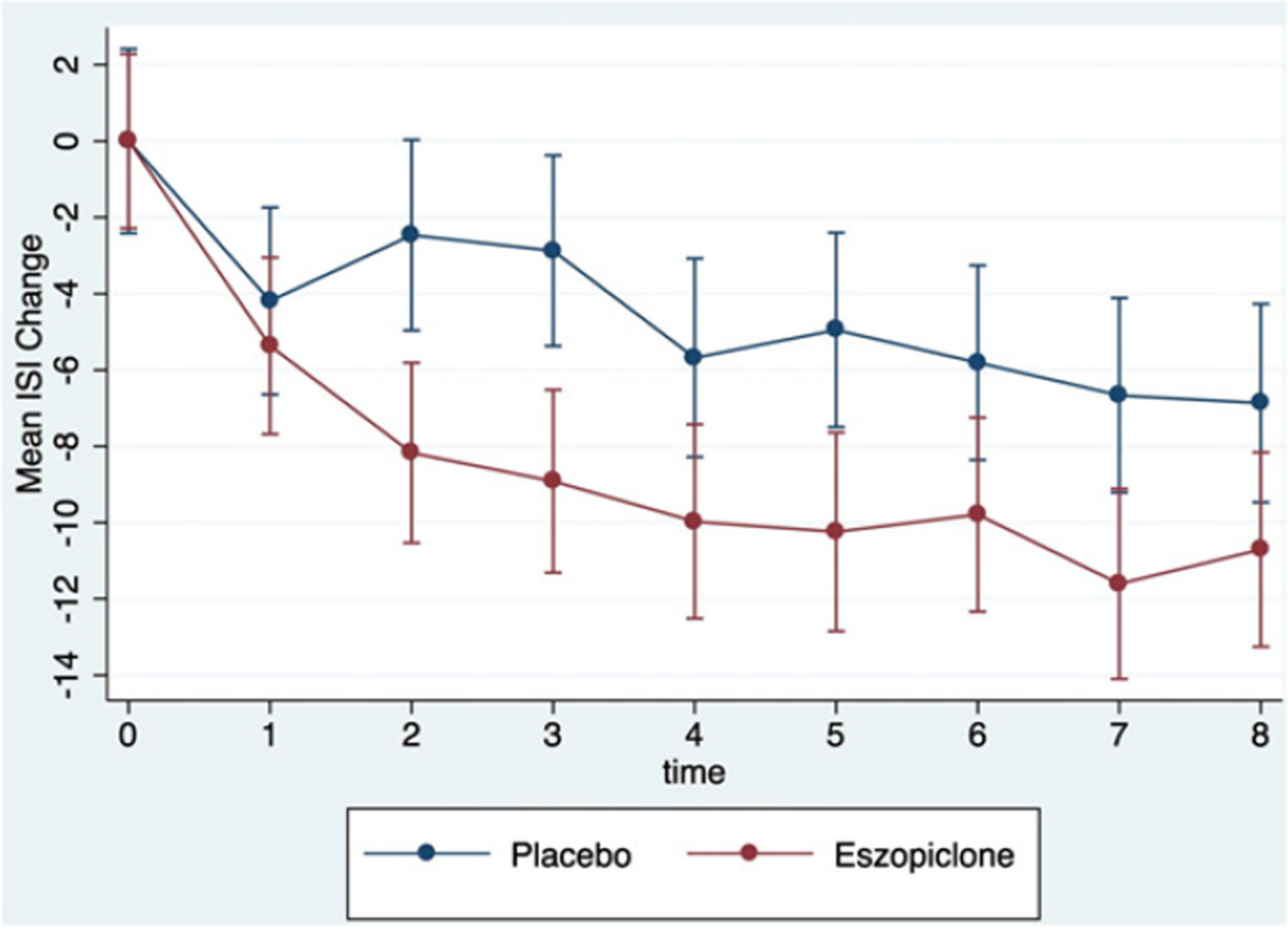

Fig. 1.

Change in total Insomnia Severity Index scores across the double-blind phase with eszopiclone or placebo. Least square means predicted from the mixed model. Error bars represent 95% confidence intervals. Significantly different between groups across the double-blind phase from baseline to week 8 ($p = 0.039$).

Table 1

Baseline demographic and clinical characteristics.

Characteristic	Eszopiclone *n* = 19		Placebo *n* = 17	
	n	**%**	***n***	**%**
Sex				
Male	10	52.6	8	47.1
Female	9	47.4	9	52.9
Occupational status				
Part-time employed	3	15.8	2	11.8
Unemployed	17	94.2	15	88.2
Diagnosis				
Schizophrenia	9	47.4	11	64.7
Schizoaffective	10	52.6	6	35.3
First generation antipsychotic use	4	21	3	17.6
Anticholinergic use[a]	6	31.6	5	29.4
	Mean	SD	Mean	SD
Age (years)	45.7	7.4	47.5	10.2
Years of education	12.5	2.1	13.3	3.5
Length of illness (years)	22.7	11.8	22.1	7.5
Chlorpromazine equivalent dose	536.38	390.26	780.29	579.63
ISI-total	17.5	4.5	15.5	3.5
Overall quality of sleep[b]	2.8	0.9	2.3	0.8
General feeling upon rising[b,*]	2.7	0.6	1.8	0.8
Daytime fatigue[b]	2.5	0.9	2.5	0.8
Concentration[b]	2.4	0.7	1.9	1.0
Relationship with others[b]	2.2	1.1	1.7	1.2
Mood disturbances[b]	2.5	1.2	1.9	1.1
Sleep latency (min)	39.9	37.6	47.7	48.9
Total sleep time (min)	378.3	143.8	367.3	135.7
Wake time after sleep onset (min)	53.4	65.2	48.9	34.6
Number of awakenings	2.4	1.6	2.5	1.3
Daytime alertness[c]	5.7	2.1	6.1	1.7
Ability to concentrate[c]	6.1	2.4	6.4	1.9
Physical well-being[c]	6.2	2.3	6.6	2.1
Ability to function[c]	5.9	2.3	6.6	2.1
PANSS-negative	14.5	4.5	15.3	4.1
PANSS-positive	14.8	3.9	17.8	4.6
PANSS-general[**]	29.4	6.9	31.4	5.8
PANSS-total	59.2	13.5	64.4	11.4

Characteristic	Eszopiclone *n* = 19		Placebo *n* = 17	
	n	**%**	***n***	**%**
CDS-total	6.6	5.4	5.3	3.7
QLES-Q-18-total	61.5	11.0	62.4	12.8

ISI = Insomnia Severity Index; PANSS = Positive and Negative Syndrome Scale; CDS = Calgary Depression Scale; QLES-Q-18 = The Quality of Life Enjoyment and Satisfaction estionnaire—Abbreviated Version.

[a] Number of participants using benztropine.

[b] Items were rated on a 5 point Likert scale (0–4) with higher scores indicating worse functioning.

[c] Items were rated on a 11 point Likert scale (0–10)with higher scores indicating better functioning.

* $p = 0.0008$.

** $p = 0.0511$.

Table 2

Change from baseline to 8 weeks in double blind period for primary and secondary outcomes.

	Eszopiclone *n* = 19		Placebo *n* = 17		Between group difference		
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	***p***
Primary outcome							
ISI-total	−10.7	−13.2; −8.2	−6.9	−9.5; −4.3	−3.8	−7.5; −0.2	0.039
Additional items							
Overall quality of sleep[a]	−1.2	−1.7; −0.6	−0.7	−1.2; −0.2	−0.5	−1.2; 0.3	0.240
General feeling upon rising[a]	−1.0	−1.5; −0.5	−0.2	−0.6; 0.3	−0.8	−1.5; −0.2	0.013
Daytime fatigue[a]	−1.0	−1.6; −0.5	−0.7	−1.3; −0.2	−0.3	−1.1; 0.5	0.478
Concentration problems[a]	−1.4	−1.9; −0.9	−0.6	−1.1; −0.1	−0.8	−1.5; −0.1	0.025
Relationship with others[a]	−1.4	−1.9; −0.8	−0.7	−1.2; −0.1	−0.7	−1.5; 0.1	0.074
Mood disturbances[a]	−1.5	−2.2; −0.7	−0.6	−1.3; 0.2	−0.9	−1.9; 0.1	0.072
Sleep diary items							
Sleep latency (min)	−18.3	−33.0; −3.5	−19.6	−34.8; −4.4	1.3	−19.9; 22.5	0.903
Total sleep time (min)	85.6	36.1; 135.2	89.2	37.4; 141.1	−3.6	−75.3; 68.2	0.922
Wake time after sleep onset (min)	−32.6	−55.4; −9.8	−23.8	−47.4; −0.1	−8.8	−41.7; 24.1	0.600
Number of awakenings	−0.9	−1.4; −0.4	−0.8	−1.4; −0.2	−0.1	−0.9; 0.7	0.817
Alertness item[b]	1.2	0.4; 2.0	1.5	0.6; 2.3	−0.3	−1.5; 0.9	0.649
Ability to concentrate[b]	0.9	0.2; 1.7	1.0	0.2; 1.7	−0.1	−1.1; 1.1	0.952
Physical well-being[b]	0.9	0.2; 1.6	0.8	0.1; 1.5	0.1	−0.9; 1.1	0.863
Ability to function[b]	1.2	0.5; 1.9	0.6	−0.2; 1.3	0.6	−0.4; 1.7	0.233
Weight (kg)	0.01	−4.3; 4.2	0.2	−3.8; 4.3	−0.2	−6.1; 5.6	0.939
Clinical rating scores							
PANSS-negative	−0.9	−2.2; 0.5	−0.7	−2.0; 0.6	−0.2	−2.1; 1.8	0.883
PANSS-positive	−3.1	−4.3; −1.8	−1.7	−2.9; −0.5	−1.4	−3.1; 0.4	0.127
PANSS-general	−2.1	−4.5; 0.2	−2.5	−4.8; −0.2	0.4	−2.9; 3.7	0.803
PANSS-total	−6.4	−10.6; −2.3	−5.1	−9.1; −1.1	−1.3	−7.2; 4.4	0.640
CDS-total	−2.5	−4.2; −0.8	−2.1	−3.7; −0.5	−0.4	−2.8; 1.9	0.730

	Eszopiclone *n* = 19		Placebo *n* = 17		Between group difference		
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	***p***
QLES-Q-18-total	0.2	−4.9; 5.4	0.8	−4.4; 6.0	−0.6	−7.9; 6.8	0.878

ISI = Insomnia Severity Index; PANSS = Positive and Negative Syndrome Scale; CDS = Calgary Depression Scale; QLES-Q-18 = The Quality of Life Enjoyment and Satisfaction Questionnaire—Abbreviated Version.

[a]Items were rated on a 5 point Likert scale (0–4) with higher scores indicating worse functioning.

[b]Items were rated on a 11 point Likert scale (0–10) with higher scores indicating better functioning.

Table 3

Cognitive domain scores at baseline, week 8, and week 10.[a]

	Baseline				Week 8				Week 10			
	Eszopiclone		Placebo		Eszopiclone		Placebo		Eszopiclone		Placebo	
Cognitive domains	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Processing speed	39.85	17.71	35.57	12.28	39.54	15.73	37.29	10.48	38.92	15.74	38.92	9.80
Attention	34.92	14.17	34.36	9.23	38.08	12.89	32.64	11.13	41.42	13.99	37.92	10.11
Working memory	32.23	17.39	34.86	12.92	37.38	14.67	35.29	10.71	33.08	15.03	36.92	9.78
Verbal learning	40.69	10.23	36.07	7.65	37.92	9.03	36.57	10.79	37.38	9.94	37.08	7.33
Visual learning	31.69	14.21	38.71	15.67	35.54	17.01	34.93	10.45	33.54	18.10	33.92	11.42
Social cognition	40.00	14.29	30.07	10.53	37.23	17.25	29.50	8.54	37.85	19.45	30.08	9.38
Reasoning/problem Solving	39.54	9.73	43.00	10.82	39.15	9.87	44.79	10.57	41.54	10.84	45.00	11.33
Composite score	28.77	19.49	27.43	13.02	32.00	18.02	27.14	13.27	31.83	18.97	29.00	11.50

All scores are T-scores (adjusted for age and gender). Baseline to week-8 is the double-blind phase. Week-8 to week-10 is the single-blind placebo phase.

[a]Analyses include only the patients who completed the 10 week study period.