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MICRO REPORT

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Suvorexant for insomnia in patients with psychiatric disorder: A 1-week, open-label study

Taro Kishi[1] | Kenji Sakuma[1] | Makoto Okuya[1] | Kohei Ninomiya[1] | Kazuto Oya[1] | Momoko Kubo[1,2] | Yuki Matsui[1,3] | Ikuo Nomura[1,4] | Yuji Okuyama[1,4] | Shinji Matsunaga[1,5] | Nakao Iwata[1]

[1]Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

[2]Department of Psychiatry, The Okehazama Hospital, Toyoake, Aichi, Japan

[3]Department of Psychiatry, The Jindai Hospital, Toyota, Aichi, Japan

[4]Department of Psychiatry, The Moriyama General Mental Hospital, Nagoya, Aichi, Japan

[5]Department of Geriatrics and Cognitive Disorders, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

Correspondence
Taro Kishi, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan.
Email: tarok@fujita-hu.ac.jp

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Abstract

Aim: There have been no previous reports on the efficacy and safety of suvorexant for insomnia in people with psychiatric disorders.

Methods: This one-week, prospective, single-arm, clinical trial of fixed dose of suvorexant (20 mg if ages 18–64 or 15 mg if age ≥ 65 years) for insomnia included 57 patients with psychiatric disorders who had experienced any of the following insomnia symptoms for four or more nights during the week prior to the start of the study: total sleep time (TST) <6 hours, time to sleep onset (TSO) ≥30 minutes, or two or more episodes of wake after sleep onset.

Results: The mean age of the patients was 49.4 ± 17.3 years; 54.4% were women, 49.1% had a major depressive disorder, and 77.2% completed the trial. Compared with the baseline scores (the mean scores for the two days before the start of the study), taking suvorexant was associated with significant improvements in TST, TSO, wake time after sleep onset, and the patients' sleep satisfaction level at week 1. Adverse events included at least one adverse event (43.9%), sleepiness (28.8%), fatigue (11.5%), nightmares (5.8%), headache (3.8%), dizziness (3.8%), and vomiting (1.9%).

Conclusion: Suvorexant was beneficial for the treatment of insomnia in people with psychiatric disorders. However, this study was of short duration and included only a relatively small number of patients. A larger, long-term study is needed to investigate the efficacy and safety of suvorexant for insomnia in people with psychiatric disorders.

KEYWORDS
efficacy, insomnia, psychiatric disorder, safety, suvorexant

Registry and the Registration No. of the study/trial: UMIN000024941

1 | INTRODUCTION

Insomnia is one of the most common symptoms experienced by people with psychiatric disorders.[1–3] Recent treatment guidelines for primary insomnia recommend both pharmacological and nonpharmacological treatments.[4] The pharmacological treatments include benzodiazepine receptor agonists, such as benzodiazepine and Z drugs, a melatonin receptor agonist, or an orexin receptor antagonist. Although benzodiazepine receptor agonists have been shown to improve symptoms related to sleep disturbance, associated adverse effects include sedation, residual effects, falls, amnesia, rebound insomnia, and physical and behavioral dependence.[5] It has been reported that ramelteon reduces latency to persistent sleep but not sleep maintenance.[6] Adverse effects associated with ramelteon include somnolence, fatigue, dizziness, and nausea; however, residual effects, rebound insomnia, and withdrawal syndrome have not been observed.[5] Our previous meta-analysis showed that suvorexant was effective in treating symptoms related to sleep disturbance and was well tolerated, similar to ramelteon.[7]

However, the efficacy and safety of suvorexant for treating insomnia in people with psychiatric disorders has not been investigated. We therefore conducted a one-week, prospective, single-arm, fixed-dose clinical trial of suvorexant for insomnia in people with psychiatric disorders.

2 | MATERIALS AND METHODS

This study was registered in the UMIN Clinical Trials Registry as UMIN000024941.

2.1 | Subjects

The study took place from November 2016 to May 2018 at Fujita Health University Hospital. It included both female and male outpatients aged ≥ 20 years who attended the Department of Psychiatry in Fujita Health University Hospital and who had experienced any of the following insomnia symptoms for four or more nights during the week before they started the study: total sleep time (TST) <6 hours, time to sleep onset (TSO) ≥30 minutes, or two or more episodes of wake after sleep onset. We assessed in the interview whether the patients met these criteria. The following exclusion criteria were applied: taking any sleeping pills other than ramelteon, zolpidem, zopiclone, or eszopiclone at baseline; contraindication to suvorexant; addiction to psychostimulants or alcohol; pregnancy or breastfeeding; neurological or systemic diseases; and anyone considered inappropriate to participate by the attending physician. We did not include any patient who received benzodiazepines before the study because sleeping pills other than the Z drugs (zolpidem, zopiclone, or eszopiclone) or ramelteon (ie, benzodiazepines are associated with a clear risk of withdrawal symptoms[5]).

The clinical trial was described in detail to the subjects, and all provided written informed consent. The study was approved by the Ethics Committee of Fujita Health University (HM17-012).

2.2 | Procedures

All the subjects received a fixed dose of suvorexant (20 mg if ages 18-64 or 15 mg if age ≥ 65 years) for seven consecutive nights. If a subject was taking Z drugs or ramelteon at baseline, these were discontinued on study day 1. Other psychotropic drugs, such as antidepressants, antipsychotics, mood stabilizers, and anxiolytics, were maintained at the same dose throughout the study.

2.3 | Efficacy and safety outcomes

The primary outcome of the study was the improvement in TST using self-reported sleep diary. Other efficacy outcomes were improvements in TSO, wake time after sleep onset, the subjects' reported sleep satisfaction level, and the severity of their psychiatric disorder. Sleep satisfaction was measured using a visual analog scale (VAS), with 0 = very poor, 5 = average, 10 = excellent. The severity of mental illness was measured using a VAS, with 0 = extremely ill and 10 = no symptoms. The safety outcomes were the discontinuation rate and the incidence of individual adverse events. Treatment-emergent adverse events were recorded, including any that occurred immediately before the study, based on both spontaneous complaints by the subjects and clinical observations. The Udvalg for Kliniske Undersøgelser Side Effect Rating Scale[8] was used for this.

The subjects were assessed for all the efficacy outcomes during the two days before they started the trial, and baseline scores were calculated as the mean for the two days. The subjects were also assessed for all outcomes at the endpoint (study day 7 or the time they discontinued the study).

2.4 | Statistical analysis

Changes in the efficacy scores between the baseline and endpoint were evaluated. All the analyses were performed using data from the full analysis set, defined as all the subjects included in the study who received at least one dose of suvorexant and underwent at least one assessment after administration of suvorexant. Missing data were replaced by using the last observation carried forward method. The number of subjects included in the study was small, so we used nonparametric statistics. This was because data histograms for small sample sizes may not be smooth even when the data are normally distributed. The Wilcoxon signed rank test was used to evaluate the statistical significance of change in the efficacy scores between the baseline and endpoint. To examine the impact of the prior use of sleeping pills on the results of this study, a subgroup analysis was performed to compare the subjects who were taking any sleeping pills at baseline with those who were not. The Wilcoxon rank-sum test for continuous variables and chi-square test for dichotomous variables were used for the subgroup analysis. Calculations were performed using JMP software (JMP 5.2. 1J, SAS Japan Inc.). A P value < 0.05 was considered to denote statistical significance.

TABLE 1 Efficacy results

	Mean scores ± SD at baseline (n = 57)	Mean change scores ± SD (n = 52)	*P* value
Total sleep time (h)	5.39 ± 2.52	1.71 ± 1.73	<.0001
Time to sleep onset (min)	52.2 ± 49.6	−22.1 ± 48.1	.0003
Wake time after sleep onset (min)	63.4 ± 67.1	−38.7 ± 44.8	<.0001
Patients' sleep satisfaction level	3.72 ± 2.58	0.70 ± 2.33	.0349
Severity of mental illness	4.54 ± 2.87	0.53 ± 2.07	.165

Abbreviation: SD, standard deviation.

3 | RESULTS

In total, 57 subjects were recruited. The mean age was 49.4 ± 17.3 years, 31 (54.4%) were female, and 28 (49.1%) had a major depressive disorder (Table S1). The types of sleeping pills taken by subjects before the start of the study were as follows: eszopiclone, 15 (26.3%); ramelteon, 1 (1.8%); zolpidem, 7 (12.3%); and zopiclone; 1 (1.8%). Of the 57 subjects, 44 (77.2%) completed the trial. The reasons for discontinuation the study were as follows: adverse events, 7 (12.2%), which included sleepiness (3), sleepiness and fatigue (1), fatigue (1), nightmares (1), and vomiting (1); lost to follow-up, 3 (5.3%); inefficacy, 2 (3.5%); and withdrawal of consent, 1 (1.8%). The subgroup analysis showed no significant differences in any of the measures at baseline between the subjects who received sleeping pills before the study and those who did not (Table 1).

We did not collect data on study discontinuation for five of the subjects, so 52 subjects were included in the full analysis set analysis. Taking suvorexant was associated with significant improvements compared with the baseline values in TST, TSO, wake time after sleep onset, and the subjects' reported sleep satisfaction levels at week 1 (Table 1). The subgroup analysis showed that suvorexant improved TST and wake time after sleep onset in the subjects who received sleeping pills before the study and TST, TSO, and wake time after sleep onset in those who did not, with no significant differences in any efficacy outcome between the two subgroups (Table S2).

Adverse events reported with taking suvorexant included at least one adverse event (43.9%), sleepiness (28.8%), fatigue (11.5%), nightmares (5.8%), headache (3.8%), dizziness (3.8%), and vomiting (1.9%). No serious psychiatric symptoms, such as psychomotor excitement, suicidal behavior, or death, were reported during the study.

4 | DISCUSSION

Suvorexant improved sleep disturbance (both sleep onset and sleep maintenance) in the subjects with psychiatric disorders. However, although suvorexant improved symptoms related to both sleep onset and sleep maintenance for the subjects who did not take sleeping pills before the study, it improved only sleep maintenance in the subjects who had been taking sleeping pills. It has been reported that Z drugs are associated with withdrawal symptoms.[5] Such symptoms could potentially act as a confounding factor that influences the improvement of sleep onset by suvorexant, possibly explaining why there was no significant improvement in TSO in the subjects who were taking sleeping pills before the study. We speculate that suvorexant might be effective for treating the disturbance of sleep onset after such withdrawal symptoms have improved. Overall, the findings of this study indicated that suvorexant had a benefit for the treatment of insomnia in patients with psychiatric disorders. However, 12.2% patients of the subjects discontinued the study because of adverse events (especially sleepiness).

One of the main limitations of this study was the small sample size. The study included patients with different psychiatric disorders and medications; this cannot be ruled out as a possible confounding factor. In addition, the trial did not include a control arm with placebo or active treatment, it was not randomized, and the subjects and physicians were not blinded to the subgroup assignment of the subjects. Because there was no control group, the efficacy and safety measures of suvorexant observed in this study could not be compared with those for other sleeping pills in this patient population. Finally, the duration of the study was short (7 days).

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CONFLICT OF INTEREST

The authors have declared that there are no conflicts of interest in relation to the subject of this study. We have had the following interests within the past 3 years. Dr. Kishi has received speaker's honoraria from Daiichi Sankyo, Dainippon Sumitomo, Eisai, Janssen, Otsuka, Meiji, MSD, Yoshitomi, and Tanabe-Mitsubishi and has received a Health Labour Sciences Research Grant, Grant-in-Aid for Scientific Research (C), and a Fujita Health University School of Medicine research grant. Dr. Sakuma has received speaker's honoraria from Eisai, Kissei, Meiji, Otsuka and Torii and has received a grant-in-aid for Young Scientists (B). Dr. Okuya has received speaker's honoraria from Meiji and Torii. Dr. Ninomiya has no conflict of interest relationship with any company. Dr. Oya has received speaker's honoraria from Chugai, Dainippon Sumitomo, Eisai, Janssen, Kissei, Meiji, MSD, Otsuka, and Tanabe-Mitsubishi. Dr. Kubo has no conflict of interest relationship with any company. Dr. Matsui has received speaker's honoraria from Dainippon Sumitomo, Janssen, and Meiji. Dr. Nomura has received speaker's honoraria from Meiji, MSD, Janssen, Otsuka, and Torii. Dr. Okuyama has no conflict of interest relationship with any company. Dr. Matsunaga has received speaker's honoraria from Daiichi Sankyo, Dainippon Sumitomo, Eisai, Janssen, Meiji, MSD, Novartis, Otsuka, and Tanabe-Mitsubishi

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DATA AVAILABILITY

The entirety of the patient's data cannot be made publicly available as data sharing was not included in the consent.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of Fujita Health University (HM17-012).

INFORMED CONSENT

The clinical trial was described in detail to the subjects, and all provided written informed consent.

ORCID

Taro Kishi https://orcid.org/0000-0002-9237-2236

REFERENCES

1. Monti JM, Monti D. Sleep disturbance in schizophrenia. Int Rev Psychiatry. 2005;17(4):247–53.
2. Mendlewicz J. Sleep disturbances: core symptoms of major depressive disorder rather than associated or comorbid disorders. World J Biol Psychiatry. 2009;10(4):269–75.
3. Plante DT, Winkelman JW. Sleep disturbance in bipolar disorder: therapeutic implications. Am J Psychiatry. 2008;165(7):830–43.
4. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an american academy of sleep medicine clinical practice guideline. J Clin Sleep Med. 2017;13(2):307–49.
5. Roehrs T, Roth T. Insomnia pharmacotherapy. Neurotherapeutics. 2012;9(4):728–38.
6. Mets MA, van Deventer KR, Olivier B, Verster JC. Critical appraisal of ramelteon in the treatment of insomnia. Nat Sci Sleep. 2010;2:257–66.
7. Kishi T, Matsunaga S, Iwata N. Suvorexant for primary insomnia: a systematic review and meta-analysis of randomized placebo-controlled trials. PLoS ONE. 2015;10(8):e0136910.
8. Jordan S, Knight J, Pointon D. Monitoring adverse drug reactions: scales, profiles, and checklists. Int Nurs Rev. 2004;51(4):208–21.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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