

The effect of lemborexant for insomnia disorder

SAGE Open Medicine

Volume 9: 1–4

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DOI: 10.1177/20503121211039098

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Abstract

Background: Lemborexant has a low dependence potential, less muscle relaxant effect, and less effect on cognitive function. However, there have been no naturalistic reports in Japan clarifying the effect of lemborexant on insomnia disorder. We retrospectively examined the effectiveness of treatment with lemborexant.

Methods: Insomnia was assessed using the Athens Insomnia Scale (AIS). Efficacy outcome assessment was the Clinical Global Impressions–Improvement scale (CGI-I).

Results: We analyzed 150 patients (male/female=57/93) in total. The mean subject age and mean duration of illness were 47.8 ± 19.9 years and 4.2 ± 7.2 years, respectively. The average dose of lemborexant was 5.9 ± 2.0 mg. The mean AIS total score was a significant improved (6.6 ± 3.7 – 3.9 ± 3.3) ($p < 0.01$). The mean CGI-I score was 3.2 ± 0.8 . The 24-week continuation rates for lemborexant were 86.7%.

Conclusion: Similar to the results obtained in previous studies, the CGI-I score, which is one of the objective indicators evaluated by the therapist, and the AIS, which is one of the subjective evaluations of patients, improved as well. The results of this study suggest that lemborexant may be safe and effective in patients with insomnia in real-world clinical practice.

Keywords

Lemborexant, benzodiazepine hypnotics, efficacy, insomnia

Date received: 26 April 2021; accepted: 24 July 2021

Introduction

Benzodiazepine hypnotics are frequently used in real-world clinical practice but are notorious for their various adverse effects, such as their addictive potential, withdrawal symptoms, cognitive impairments, and dementia, as well as increased mortality, especially in the elderly.¹ They are also known to cause these patients to fall, causing fractures. Furthermore, benzodiazepine hypnotics have a high risk of tolerance and dependence; therefore, it is often difficult to reduce or suspend their dosage.^{2,3} Therefore, it is often difficult to reduce the dose of or suspend benzodiazepine hypnotics. However, the mechanism of action of lemborexant involves the competitive antagonism of the orexin receptor, which may be involved in the stabilization of wakefulness. This is thought to reduce its impact on the spectrum of electroencephalography (EEG) during sleep and act specifically on the sleep–wake cycle, thereby inducing physiological sleep.⁴ Lemborexant has been proven to assist the process of falling asleep and prevent nocturnal awakening. Furthermore, lemborexant has a low dependence potential, is ineffective as a muscle relaxant, and does not significantly affect

cognitive function. Therefore, it has potential as an insomnia medication that lacks the problematic side effects of other pharmacological treatment options. However, no naturalistic studies have yet been conducted in Japan to elucidate the effect of lemborexant on patients with insomnia disorder. In this study, we retrospectively analyzed the efficacy of lemborexant treatment.

Methods

Patients and study design

The participants enrolled in this retrospective study were outpatients at Suzuki Clinic. All participants were diagnosed with insomnia disorder based on the guidelines of the

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Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition, and were followed up for 6 months after their first lemborexant prescription. The observation period lasted from July 2020 (when it was introduced for clinical use) to December 2020. Furthermore, there were no criteria for the exclusion of the research subjects in this study. Insomnia was assessed using the Japanese version of Athens Insomnia Scale (AIS).^{5,6} The efficacy outcome assessment used was the Clinical Global Impressions–Improvement scale (CGI-I).⁷ The cessation of drug administration was considered an “event,” and the period leading up to the occurrence of the “event,” “closure,” or “conclusion of observation” was included in the observation period used in our statistical analysis. The reasons for the occurrence of the “event” were categorized using the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study⁸ as either “due to lack of efficacy,” “owing to intolerability,” “owing to patient’s decision,” or “for other reasons.”⁸ This study was approved by the ethics committee of Fukui Kinen Hospital on 21 January 2021 (approval no. 2-017). Furthermore, the mode of consent/opt-out recruitment was approved by Fukui Kinen Hospital. Therefore, rather than waiving informed consent for the retrospective cohort study, we posted information regarding the study in the hospital and conducted opt-out recruitment.

Statistical analysis

We compared patient background characteristics and AIS and CGI-I scores with the Mann–Whitney *U* test and estimated the treatment continuation rate using the Kaplan–Meier survival analysis. The significance level was set at $p < 0.05$.

Results

Patient characteristics

The number of recruited patients who opted out was 150 (male/female=57/93), and no one else was excluded from the study. Seventy-seven (male/female=31/46) patients had recently started lemborexant and 73 (male/female=26/47) patients had switched from benzodiazepine hypnotic monotherapy to lemborexant. The mean subject age and mean duration of illness were 47.8 ± 19.9 years and 4.2 ± 7.2 years, respectively. The patients’ comorbidities included schizophrenia ($n=2$), depression ($n=59$), bipolar disorder ($n=24$), anxiety ($n=53$), and dementia ($n=12$). The average dose of lemborexant was 5.9 ± 2.0 mg. The rate of the concomitant use of benzodiazepine anxiolytics was 29.3% ($n=44$), and the mean amount of diazepam conversion was 1.7 ± 2.4 mg. The rate of concomitant use of antidepressants was 35.3% ($n=53$), of which 41.5% ($n=22$) used selective serotonin reuptake inhibitors, 32.1% ($n=17$) used serotonin noradrenaline reuptake inhibitors, 13.2% ($n=7$) used noradrenergic

and specific serotonergic antidepressants, and 13.2% ($n=7$) used other types of antidepressants. The rate of concomitant use of mood stabilizers was 12.0% ($n=18$), among whom 61.1% ($n=11$) used lamotrigine, 33.3% ($n=7$) used lithium carbonate, and 5.6% ($n=1$) used sodium valproate. The rate of concomitant antipsychotic use was 10.7% ($n=16$), overall and the breakdown was classified based on 100% second-generation antipsychotic use.

Change of scale

The mean AIS total score improved significantly after 24 weeks of treatment (from 6.6 ± 3.7 to 3.9 ± 3.3) ($p < 0.01$). The mean CGI-I score was 3.2 ± 0.8 .

Treatment continuation rate

Because 21 patients stopped taking lemborexant due to improved insomnia, they were excluded from the continuation rate analysis. The 24-week continuation rate for lemborexant was 86.7% (Figure 1).

Reasons for discontinuation

In this study, patients discontinued treatment for the following reasons: the patient’s decision ($n=2$), lack of efficacy ($n=4$), sleepiness ($n=5$), fatigue ($n=1$), and nightmares ($n=1$). All adverse events were mild and transient and completely resolved themselves after discontinuation.

Discussion

The primary outcome measured in this study was the treatment continuation rate, which can be influenced by various factors such as the physician–patient relationship, drug efficacy, safety, and tolerability. This study was conducted under the assumption that continued medication usage meant that the treatment was progressing well. Similar to results obtained in previous studies,⁸ the 6-month continuation rate of lemborexant in this study was relatively high compared to that of other types of medication (approximately 90%). Earlier sleep onset and improved sleep maintenance have been reported in both short- and long-term studies via both objective and subjective evaluations using polysomnography and sleep diaries, respectively.⁹ Similar to results obtained in previous studies, both the CGI-I score, which is an objective indicator evaluated by therapists, and the AIS (six points or less), which is a subjective evaluation of patients, also improved. Furthermore, 21 patients in this study were able to discontinue the use of lemborexant due to improved insomnia.

In contrast, long-term administration of benzodiazepine hypnotics is not recommended because they are associated with various problems, including physical dependence and adverse effects on cognitive function, which leads to reduced

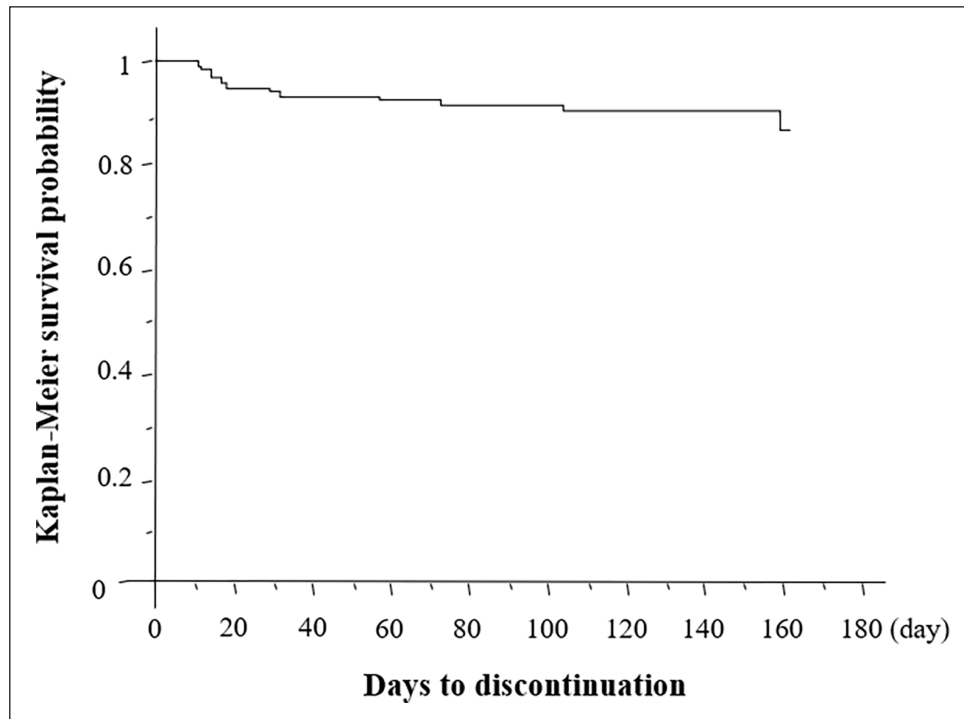


Figure 1. Kaplan–Meier analysis of time to discontinuation of lemborexant ($n = 129$).

adherence.^{2,3} The results of this study showed that the concomitant use rate and dosage of benzodiazepine anxiolytics involving the risk of falls and fractures in the elderly due to lightheadedness and cognitive decline were reduced. Lemborexant does not act via gamma-aminobutyric acid (GABA) receptors; therefore, the risk of patients developing dependence and tolerance is relatively low.¹⁰ Similar to the results of previous studies, the treatment interruption rate due to adverse events was low and no serious adverse events were observed in this study.¹¹ Previous studies suggested that lemborexant affected lightheadedness and cognitive function little when waking up. Moreover, the incidence rate of adverse events also suggests that lemborexant tolerability is good.^{10,11} Similar to the results of previous studies, the treatment interruption rate was low for adverse events and no serious adverse events were observed in this study.¹² However, it should be thoroughly explained to the patient that the sensation of falling asleep may differ from that of previously used drugs; thus, the symptoms of insomnia might be temporarily aggravated. Furthermore, we attempted to mitigate concerns and anxiety related to sleep.

However, since this study is a retrospective survey documenting actual clinical results, several points should be considered while interpreting the results. The greatest limitation of this study is that it was a short-term (up to 6 months) study and it was not double-blinded. In addition, it has a relatively small sample size because it includes all patients treated with lemborexant at the site where the data were collected and power analysis/formal sample size calculation for sample

size was not performed. The selection of subjects for drug treatment and the index for treatment continuation were also based on subjective judgments of efficacy, tolerability, and so on. Therefore, a prospective monotherapy study should be conducted to confirm our findings.

Conclusion

The results of this study suggest that lemborexant may be safe and effective in patients with insomnia in real-world clinical practice.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr H.S. has received honoraria from Janssen Pharmaceutical K.K., Otsuka Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd, and Eisai Co., Ltd. Dr H.H. has received honoraria from Janssen Pharmaceutical K.K., Otsuka Pharmaceutical Co., Ltd, and Dainippon Sumitomo Pharma Co., Ltd.

Ethics approval

This study was approved by the ethics committee of Fukui Kinen Hospital. The approval date and approval number of the ethics committee of Fukui Kinen Hospital were 21 January 2021 and 2-017, respectively. Furthermore, the mode of consent/opt-out recruitment was approved by Fukui Kinen Hospital. Therefore, the need for written consent waived off by the Ethics Committee of Fukui Kinen Hospital.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Instead of omitting the informed consent for the retrospective cohort study, information about the study was posted in the hospital, and opt-out recruitment was conducted. All subjects had decisional capacity to provide consent.

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