

Characteristics of patients who were able to switch from benzodiazepine hypnotics to lemborexant

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Abstract

Objectives: There is little evidence of insomnia treatment, especially exit strategies for hypnotics. We examined on the characteristics of patients who were able to switch from benzodiazepine hypnotics to lemborexant.

Methods: Insomnia was assessed using the Athens Insomnia Scale. Efficacy outcome assessment was the Clinical Global Impressions-Improvement scale.

Results: Eighty patients switched from benzodiazepine hypnotic monotherapy to lemborexant and 57 patients who continued the use of benzodiazepine hypnotics. The switched group had a significantly lower benzodiazepine hypnotic diazepam equivalent and a significantly shorter dosing period than the continued group ($p < 0.001$ for all). The mean Athens Insomnia Scale total score of the switched group was a significant improved (5.8 ± 3.3 to 4.0 ± 3.3 ; $p < 0.05$). The mean Clinical Global Impressions-Improvement score of the switched group was 3.3 ± 0.7 .

Conclusion: Our findings suggest that when administering benzodiazepine hypnotics, shortening the administration period, as much as possible, allows a smooth switch to safe long-term maintenance therapy using lemborexant, without exacerbating insomnia.

Keywords

Lemborexant, benzodiazepine hypnotics, efficacy, switching, insomnia

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Introduction

As an exit strategy for hypnotics, dose reduction, discontinuation, or safe long-term maintenance therapy can be used after insomnia has resolved and the patient has recovered. However, benzodiazepine hypnotics have a high risk of tolerance and dependence, and therefore, it is often difficult to reduce their dosage.^{1,2} Therefore, it is often difficult to reduce the dose of or suspend benzodiazepine hypnotics. On the contrary, the mechanism of the orexin receptor antagonist, lemborexant, has been shown to be effective for both difficulty falling asleep and nocturnal awakening.³ Furthermore, lemborexant has a low dependence potential. We reported that the use of lemborexant can subsequently lead to treatment discontinuation, which is one of the exit strategies for hypnotics, and may in turn improve drug adherence.⁴ Therefore, with regard to considering the exit strategies for hypnotics for insomnia treatment, it may be meaningful to switch from benzodiazepine hypnotics to lemborexant, which is among the safe long-term maintenance therapies. Here, we report on the characteristics of patients

who were able to switch from benzodiazepine hypnotics to lemborexant.

Methods

Patients and study design

The participants enrolled in this retrospective study were outpatients at Suzuki Clinic. All participants received the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnosis for insomnia, and were prescribed either lemborexant or benzodiazepine hypnotics. The observation period was from July 2020 (when introduced for clinical use) to December 2020 for lemborexant and

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Table 1. Subject characteristics.

	Switched group (N=80)	Continued group (N=57)	p-value
Age (years)	48.1 ± 18.7	53.6 ± 15.9	0.07
Disease duration (years)	5.4 ± 8.6	12.5 ± 12.6	<0.001
Administration period of benzodiazepine hypnotics (years)	3.9 ± 4.8	12.4 ± 12.6	<0.001
Diazepam conversion amount of benzodiazepine hypnotics (mg)	4.6 ± 2.8	8.9 ± 4.2	<0.001

benzodiazepine hypnotics. Furthermore, there were no criteria for exclusion of research subjects in this study. 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. 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. Insomnia was assessed using the Japanese version of Athens Insomnia Scale (AIS).⁵ Efficacy outcome assessment was from the Clinical Global Impressions-Improvement (CGI-I) scale.⁶

Switching method

One of the following methods was used by the patients to switch from benzodiazepine hypnotics to lemborexant:

1. Benzodiazepine hypnotics were discontinued with initiation of 5 mg of lemborexant.
2. Lemborexant (5 mg) was added to the current medication of benzodiazepine hypnotics; gradually, benzodiazepine hypnotics were tapered off while adjusting lemborexant as appropriate.
3. Lemborexant (5 mg) was started while tapering benzodiazepine hypnotics, and benzodiazepine hypnotics were discontinued while adjusting lemborexant as appropriate.

Statistical analysis

Comparison of patient background characteristics was conducted using the Mann–Whitney *U* test, which was used to compare age, disease duration (years), administration period of benzodiazepine hypnotics (years), diazepam conversion amount of benzodiazepine hypnotics (mg), AIS, and CGI-I scores. The significance level was set at $p < 0.05$.

Results

The number of recruited patients by opting out was 137 (male/female, 51/86), and the number of people who were not incorporated was 0. All patients had decisional capacity to provide consent. Of these, 80 (male/female; 29/51)

patients switched from benzodiazepine hypnotic monotherapy to lemborexant and 57 (male/female; 22/35) continued using benzodiazepine hypnotics (Table 1). None of the patients in the continued using benzodiazepine hypnotics attempted to switch from benzodiazepines to lemborexant.

The group that switched therapies experienced a significantly shorter duration of illness than the group that continued the initial therapy. The former group had a significantly lower benzodiazepine hypnotic diazepam equivalent and a significantly shorter dosing period than the latter ($p < 0.001$ for all). The average dose of lemborexant was 6.2 ± 2.2 mg. The schedule for reduction and discontinuation of the benzodiazepine hypnotic varied among patients as it was determined by the treating physician, based on the condition of each patient. The time until benzodiazepine hypnotic discontinuation was 21.9 ± 33.2 days. The mean AIS score of the switched group significantly improved (5.8 ± 3.3 to 4.0 ± 3.3 ; $p < 0.05$). The mean CGI-I score of the switched group was 3.3 ± 0.7 . The adverse effects observed in the switched group were sleepiness ($n=3$), fatigue ($n=1$), and nightmares ($n=1$). All adverse events were mild and transient and completely resolved after discontinuation of lemborexant.

Discussion

Previous studies have found that withdrawal symptoms tend to occur when multiple benzodiazepine hypnotics are discontinued and/or after long-term administration for 6 months or more.⁷ Furthermore, there have been reports of difficulties in dose reduction or suspending treatment.⁷ Long-term administration is not recommended due to various problems associated with benzodiazepine hypnotics, including physical dependence and adverse effects on cognitive function, which leads to reduced adherence. On the contrary, lemborexant does not act via gamma-aminobutyric acid (GABA) receptors, and therefore, the risks of patients developing dependence and tolerance are considered low.⁸ Furthermore, sleep-onset and sleep-maintaining effects have been reported in both short-term and long-term studies via objective evaluation using polysomnography and subjective evaluation using sleep diaries.³ In this study, the administration period of benzodiazepine hypnotics was relatively long but, similar to previous reports, the subjective evaluation improved, allowing

switching from benzodiazepine hypnotics to lemborexant at a relatively early stage. However, it should be thoroughly explained to the patient that since the sensation of falling asleep may differ from that of previous drugs, the symptoms of insomnia might be temporarily aggravated. Furthermore, we attempted to mitigate concerns and anxiety regarding sleep. However, the most prevalent side effect of lemborexant was somnolence. Most events of somnolence were mild and well tolerated, even though the increase in incidence was dose-related. In this study, the drug was well tolerated, thus corroborating previous studies.³ Therefore, our findings suggest that when administering benzodiazepine hypnotics, shortening the administration period, as much as possible, allows a smooth switch to safe long-term maintenance therapy using lemborexant, without exacerbating insomnia.

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 is a short-term (up to 6 months) study that is not a double-blind study. In addition, it has a relatively small sample size because it includes all patients treated with either lemborexant or benzodiazepine hypnotics at the site where the data were collected and power analysis/formal sample size calculation for sample size was not performed, the number of patients treated with benzodiazepine hypnotics is lower than that treated with lemborexant.

Therefore, prospective randomized controlled trials including patients who switched their medication from benzodiazepine to lemborexant and patients who continued using benzodiazepine may be needed to clarify if lemborexant is more likely to lead to treatment discontinuation than benzodiazepine hypnotics.

Conclusion

Our findings suggest that when administering benzodiazepine hypnotics, shortening the administration period, as much as possible, allows a smooth switch to safe long-term maintenance therapy using lemborexant, without exacerbating insomnia.

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.

Ethical 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. The need for written consent waived off by the Ethics Committee of Fukui Kinen Hospital.

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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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