PSYCHOLOGICAL MEDICINE

Usefulness in the Group That Switched to Lemborexant for Insomnia Disorder

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ABSTRACT

Objective: **There have been no naturalistic reports in Japan clarifying the effect of switched to emborexant on insomnia disorder. This study aimed to investigate the difference in treatment continuation between the recently started group and switched group in clinical setting.**

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

Results: **77 patients had recently started lemborexant and 73 patients switched from benzodiazepine hypnotic monotherapy to lemborexant. The mean AIS total score of the recently started group and switched group were a significantly improved (7.7 ± 4.1 to 3.7 ± 3.4; 5.7 ± 3.3 to 3.9 ± 3.3) ($p < 0.05$). There was no significant difference in the mean CGI-I scale between the recently started group and switched group (3.0 ± 0.9; 3.3 ± 0.8). Furthermore, there was no significant difference in the 24-weeks continuation rate between the recently started group and switched group.**

Conclusions: **These results indicate that the use of lemborexant may lead to safe and maintenance therapy, which is one of the exit strategies for hypnotics, and may in turn improve drug adherence.**

KEY WORDS

lemborexant, efficacy, treatment discontinuation, insomnia

INTRODUCTION

Benzodiazepine hypnotics have a high risk of tolerance and dependence and therefore, it is often difficult to reduce their dosage (Rudolph *et al*. 2011; Tan *et al*. 2011). Therefore, it is often difficult to reduce the dose of or suspend benzodiazepine hypnotics. On the other hand, the orexin receptor antagonist lemborexant has been shown to be effective for both difficulty falling asleep and nocturnal awakening. Furthermore, lemborexant has a low dependence potential, and less effect as a muscle relaxant and on cognitive function. Therefore, it represents an insomnia medication that frees the patient from some problematic side effects of pharmacological treatment. In previous research, we reported the effectiveness of lemborexant treatment (Suzuki and Hibino, 2021). However, there have been no naturalistic reports in Japan clarifying the effect of switched to emborexant on insomnia disorder. This study aimed to investigate the difference in treatment continuation between the recently started group and switched group in clinical setting.

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 of insomnia disorder and were followed up for 6 months after their first lemborexant prescription. The observation period was from July 2020 (when introduced for clinical use) to March 2021. This study was approved by the ethics committee of Fukui Kinen Hospital. Insomnia was assessed using the Athens Insomnia Scale (AIS) (Soldatos *et al*., 2000; Okajima *et al*., 2013). Efficacy outcome assessment was the Clinical Global Impressions-Improvement scale (CGI-I).

Statistical analysis

Comparison of patient background characteristics and AIS and CGI-I scores was conducted using a Mann-Whitney *U* test. The treatment continuation rate was estimated using a Kaplan-Meier survival analysis. The significance level was set as $p < 0.05$.

RESULTS

We analyzed 150 patients (male/female; 57/93) in total. 77 (male/female; 31/46) patients had recently started lemborexant and 73 (male/female; 26/47) patients switched from benzodiazepine hypnotic monotherapy to lemborexant. The mean subject age and mean duration of illness of the recently started group and switched group were 48.0 ± 21.6 years and 2.8 ± 4.6 years, and 47.8 ± 17.7 years and 5.4 ± 8.9 years, respectively. The average dose of lemborexant of the recently started group and switched group were 5.4 ± 1.6 mg and 6.3 ± 2.2 mg, respectively. The diazepam conversion amount of benzodiazepine hypnotics in the switched group was 5.0 ± 2.6 mg and the administration period was

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5.4 ± 8.9 years. The mean AIS total score of the recently started group and switched group were a significantly improved (7.7 ± 4.1 to 3.7 ± 3.4; 5.7 ± 3.3 to 3.9 ± 3.3) ($p < 0.05$). There was no significant difference in the mean CGI-I scale between the recently started group and switched group (3.0 ± 0.9; 3.3 ± 0.8). Furthermore, there was no significant difference in the 24-weeks continuation rate between the recently started group and switched group (Figure 1). The discontinued treatment for any of the reasons investigated in the recently started group and switched group were patient's decision (n = 0; n =2), insufficient efficacy (n = 3; n = 1), sleepiness (n = 2; n = 3), fatigue (n = 1; n = 0), and nightmare (n = 0; n = 1). All adverse events were mild and transient and completely resolved after discontinuation of lemborexant.

DISCUSSION

Similar to the results obtained in previous studies (Kärppä *et al*., 2020), the 6-month continuation rate of both group in the present study was comparatively high (approximately 90%). 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 (Rosenberg *et al*. 2019). Similar to the results obtained in previous studies (Rosenberg *et al*. 2019), the switched group was as effective as the recently started group, as assessed by CGI-I score, which is one of the objective indicators evaluated by the therapist, and the AIS (6 points or less), which is one of the subjective evaluations of patients. On the other hand, long-term administration is not recommended due to various problems associated with benzodiazepine hypnotics, including physical dependence and adverse effects on cognitive function. Furthermore, previous studies have found that withdrawal symptoms tend to occur when discontinuing multiple benzodiazepine hypnotics and/or after long-term administration for 6 months or more (Gorgels *et al*. 2006). However, there have been reports of difficulties in dose reduction or suspending treatment. On the other hand, lemborexant does not act via the GABA receptors, and therefore, the risks of patients developing dependence and tolerance are considered low. The results of this study suggest that the smooth switching to lemborexant was because of the following: the administration period of benzodiazepine hypnotics exceeded 6 months. However, since the diazepam conversion amount was found to be relatively low, and since insomnia had improved only to a certain extent, we made a decision, jointly with the patient, to switch diazepam to lemborexant with the aim of conducting safe and long-term maintenance therapy, which was the exit strategy of the treatment. However, it should be thoroughly explained to the patient that since the sensation of falling asleep may differ from the one previous drugs evoked, the symptoms of insomnia might be temporarily aggravated. Furthermore, we attempted to mitigate their concerns and anxiety regarding sleep.

Therefore, these results indicate that the use of lemborexant may lead to safe and maintenance therapy, which is one of the exit strategies for hypnotics, and may in turn improve drug adherence.

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