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Suvorexant as an Adjunctive Treatment for Insomnia Prior to Discontinuation of Benzodiazepines: Prevention of Withdrawal Syndrome and Rebound Insomnia

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Abstract

Objective: To examine whether concurrent use of benzodiazepines (BZDs) affects continuation rates for suvorexant.

Background: A wider range of different BZDs and similar drugs are available on prescription in Japan than in other countries, making prescribing more complicated. Safety has only been indicated for the use of suvorexant as monotherapy in primary insomnia. Understanding the safety of concurrent use of suvorexant with other drugs could simplify prescriptions for insomnia.

Material and Methods: We obtained the prescription records of patients who were hospitalized or attended outpatient appointments, and were prescribed suvorexant, at Showa University Karasuyama Hospital between November 2014 and April 2016.

Results: Patients prescribed suvorexant were retrospectively surveyed for drug discontinuation as indicated in their medical records. Among 326 patients who were prescribed suvorexant during the study period, use of the medication could not be confirmed in 20 patients, who were therefore excluded. This left a final study sample of 306 patients. We could track 289 patients up until day 90. There were no significant differences observed between patients treated with a BZD combination (54.0%) and those not treated with a combination (46.0%) in terms of medication continuation across the 90-day observation period (Exp(B)=1.304, 95% confidence interval, CI: 0.827-2.057, P=0.253). The rates of side effect onset were also not significantly different.

Conclusion: We observed that concurrent use of BZD was not related to withdrawal from suvorexant in patients being treated for insomnia.

Keywords: Insomnia; Suvorexant; Benzodiazepine; Combination therapy

Introduction

A nationwide survey in Japan reported that insomnia is experienced by 21.4% of the general adult population [1], and poses a serious problem. Insomnia can lead to cognitive impairment, loss of physical functioning during the day, major depression, and anxiety [2]. Moreover, approximately 20% of severe injuries in traffic accidents are said to stem from the sleeplessness of drivers, and insomnia is reported as a trigger of serious accidents and economic loss [3]. Given these findings, effective treatment for insomnia is necessary.

In Japan, a wider range of different benzodiazepines (BZD) and similar drugs are available for prescription compared with other countries, making prescribing more complicated [4]. However, few studies have surveyed the efficacy of long-term administration of BZD [5,6] and reported negative outcomes. Furthermore, although both antidepressants and antipsychotics have been used to treat insomnia [7], the safety of long-term use of each drug alone, as well as their concurrent use, has not been demonstrated [8].

To ameliorate the problems related to the complexities of prescribing for insomnia, Japanese clinicians have been working to identify ways to simplify prescriptions for the condition. For patients using BZD over a long period, sudden discontinuation can elicit rebound insomnia [9], which may exacerbate chronic insomnia or encourage increased dosages of sleep medications. To support clinicians, guidelines for appropriate use of sleep medications have been formulated, and various initiatives have been developed in Japan (Figure 1).

Suvorexant, which has a completely different mechanism of action than does BZD, may provide a way to simplify prescriptions for insomnia in Japan. In 2014, suvorexant was approved by the US Food and Drugs Administration (FDA) for use in insomnia, given its observed efficacy [10]. In the same year, sales of the drug began on November 26 in Japan, ahead of other countries [11]. In Japan, BZD constitute the first-line sleep medication, with action at $GABA_A$ receptors. In contrast, suvorexant is a selective dual orexin receptor antagonist (DORA), which acts antagonistically at both orexin receptor 1 and orexin receptor 2, inhibiting arousal nuclei that are controlled by orexin neurons to induce sleep [12,13]. In a phase 3 randomized controlled trial, Michelson et

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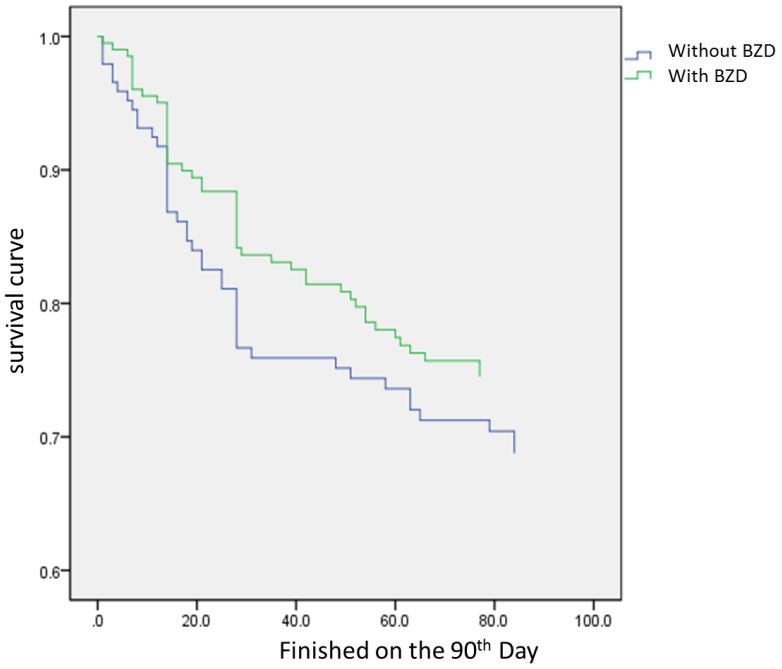

Figure 1: Survival function for the average value of the covariates.

al. [14] have reported longer total sleep duration and reduced sleep onset latency 1 month after first administration, with clear sleep-promoting effects observed from the first night of administration in the suvorexant-treated group. It is supposed that suvorexant will cause less dependence compared with conventional sleeping drugs as it does not act on GABA receptors, and is thus considered safer. Indeed, in a clinical trial, no significant difference was observed in the test group regarding withdrawal syndrome and rebound insomnia when they withdrew from the drug compared with the placebo-controlled group.

When BZDs are used in combination with several other drugs, discontinuing BZD all at once and replacing them with suvorexant could cause difficulties as it carries a high risk of inducing withdrawal symptoms. If suvorexant can be administered to users of BZD in a safe manner, BZD could then be withdrawn after the additional administration of suvorexant.

However, safety information concerning the concurrent use of suvorexant with other drugs is currently lacking. Safety has been indicated for the use of suvorexant as monotherapy for primary insomnia. However, efficacy and safety of its administration in secondary insomnia or in combination with other drugs have not been confirmed [15]. The symptoms of insomnia are also commonly experienced in psychiatric disorders, and therefore, it is important to ensure adequate sleep duration in parallel with the treatment of primary disease. Although several such cases have been reported [16,17], no studies have been conducted investigating multiple cases of secondary insomnia. Therefore, accumulating data concerning the safety and efficacy of suvorexant, including its use in secondary insomnia and concurrent use of other drugs, is necessary.

The purpose of the present study was to retrospectively survey medical records of patients who have been prescribed suvorexant for insomnia at our facility, and to examine whether concurrent use of BZD affects continuation rates for suvorexant. We hypothesized that concurrent use of BZD would not affect the continuous administration of suvorexant.

Material and Methods

Data source

We used prescription records from outpatient and inpatient treatment at the Showa University Karasuyama Hospital as our data source.

Selection of study participants

We obtained the prescription records of patients who were hospitalized or attended outpatient appointments, and were prescribed suvorexant, at Showa University Karasuyama Hospital between November 2014 and April 2016. From these patients, we included those who had taken suvorexant at least once, adhering to the prescribed dosage and administration. The day on which the drug was prescribed was designated as the first day of administration. We excluded patients who had not taken the drug or who had used it inappropriately.

Study design

Patients starting suvorexant were retrospectively surveyed for drug discontinuation as indicated in the medical records. We designated an observation period of 90 days from the first day of administration of suvorexant.

We collected data regarding each patient's age, their primary diagnoses (based on the International Classification of Disease, ICD-10), inpatient or outpatient status, initial dosage of suvorexant, any concurrently used antipsychotics, the presence of side effects, and the reason for discontinuation.

The day on which suvorexant was withdrawn from the

		BZDs combination group (n=166)	BZDs non-combination group (n=140)	Total
	P value	n	n	n
Sex	0.41			
Male		64	63	127
Female		102	77	179
Age (mean ± SD)	<0.05	49.3 ± 16	58 ± 22.9	53.4 ± 20
Patient	<0.05			
Inpatient		57	78	135
Outpatient		109	62	171
Diagnostic code	<0.05			
F0		4	49	53
F1		16	13	29
F2		36	22	58
F3		66	28	94
F4		20	14	34
F5		2	1	3
F6		6	4	10
F7		3	1	4
F8		4	5	9
F9		9	3	12
Dose	<0.05			
15 mg		52	92	144
20 mg		114	48	162
Concurrent	0.84			
Yes		107	91	198
No		48	43	91

Table 1: Patient characteristics across all groups.

prescription after the initiation of the drug was designated as the suvorexant discontinuation day. The observation period for cases of discontinuation was designated as the number of days until the day of discontinuation. We also designated patients as discontinuation cases where prescription changes could not be traced due to the transfer of the patient to another hospital during the observation period. Patients who continued to follow the prescription until day 90 were designated as the drug continuation group.

We also identified patients who were prescribed BZD or BZD-like drugs simultaneously with the initiation of suvorexant (BZD combination group), and those who were not prescribed BZD (non-combination group).

Data analysis

We used χ^2 and Student's t-tests to examine any significant differences in patient characteristics between patients in the BZD combination and non-combination groups. We analyzed treatment continuation rates in the BZD combination and non-combination groups to examine whether concurrent use of BZD is associated with suvorexant continuation. We conducted a survival analysis, which takes drug discontinuation as an event. The period from the start of treatment to day 90 was analyzed using Cox proportional hazards. We adjusted for patient background factors for which a difference was observed between the groups. In addition, the log-rank test was used to compare the BZD combination and non-combination groups. Results where $P<0.05$ were designated as significant. The baseline functions of the Cox proportional hazards model that were created were used to create a survival curve and the treatment continuation rates of both groups were estimated. All analyses were conducted with SPSS Statistics Version 22.

Ethical considerations

This research was approved by the internal review board of the Showa University Karasuyama Hospital (B-2016-027). There are no conflicts of interest for any authors to be declared in relation to this study.

Results

Patient characteristics

Among 326 patients who were prescribed suvorexant during the study period, use of the medication could not be confirmed in 20 patients, who were therefore excluded. This left 306 patients as the study sample. We could track 289 patients up until day 90. We were unable to track the remaining 17 patients for several reasons, including hospital transfer. Table 1 presents the characteristics for all patients, as well as those for each group (BZD combination and non-combination groups).

Factors associated with combination treatment

We compared the characteristics of the BZD combination and non-combination groups. There was no significant difference observed in sex. However, the BZD combination group were significantly younger,

had higher suvorexant doses (20 mg), and a higher rate of outpatient prescription than did the non-combination group. There was also a significant difference observed in patient diagnoses, with higher rates of F3 (mood disorders) in the BZD combination group, but higher rates of F0 (organic mental disorders) in the non-combination group.

Continuation rates in the BZD combination and non-combination groups

We adjusted for patient characteristics in which differences were observed between the BZD combination and non-combination groups in the Cox proportional hazards model, which was used to create a survival curve. We estimated the medication continuation rate from the start of medication up to day 90 for each group (Figure 1).

The continuation rates were 54.0% and 46.0% for the BZD combination and non-combination groups, respectively. In addition, there was no significant difference observed between the BZD combination and non-combination groups in terms of medication continuation across the 90-day observation period (Exp(B)=1.304, 95% confidence interval, CI: 0.827-2.057, P=0.253).

Onset of side effects

Table 2 presents side effects observed during the study period. The rates of side effect onset were 13.3% (22 subjects) and 17.1% (24 subjects) for the BZD combination and non-combination groups, respectively. These rates were not significantly different. All side effects showed rapid improvement after stopping the drug.

Symptom	With BZD (n=22, 13.3%)	Without BZD (n=24, 17.1%)	Total (n=46)
Over-sedation	8	15	24
Worsening sleep	3	2	4
Nightmare	2	2	4
Dizziness	2	2	3
Lightheadedness	0	2	3
Malaise	1	1	2
Rash	2	0	2
Delusion	2	0	2
Tightness in the head	1	0	1
Groaning in sleep	1	0	1
Nausea	0	1	1
Mood swings	1	0	1
Stickiness in the mouth	1	0	1
Auditory hallucinations	0	1	1
Dry mouth	1	0	1
Reversal of day and night	0	1	1
Thirst	0	1	1
Chest pain	0	1	1
Temporary feeling of paralysis	1	0	1

Table 2: Onset of side effects in both groups (multiple responses).

Discussion

In this study, we retrospectively examined suvorexant continuation rates between two patient groups: those undergoing BZD combination therapy and those without combination therapy. Our findings indicated a continuation rate of suvorexant medication after 90 days of 54.0% for the BZD combination group and 46.0% for the non-combination group. These rates were not significantly different. We observed that, compared with the non-combination group, patients in the BZD combination group were younger, had a higher dose (mean 20 mg higher), and a higher rate of outpatient prescriptions and diagnosis. However, no significant difference was observed in the drug continuation rate between the groups, even when adjusting for these factors. These findings suggest that suvorexant can be continually administered even in combination with BZD. Furthermore, this study suggests that approximately half of patients treated with suvorexant concurrently take BZD, and suvorexant is often used in combination with BZD in actual clinical practice. Hence, our results demonstrate the safety of concurrent use of suvorexant with BZD.

No significant difference was observed between the groups regarding side effects, and no serious side effects were observed in either group. These findings suggest that suvorexant can be safely used in combination with BZD. Some side effects have been observed in 50% of those who took eszopiclone, which was expected to be relatively safer among BZD, in a parallel-group trial conducted overseas. In contrast, only 20.9% of patients developed side effects during six months' administration of suvorexant in a Phase III international joint trial. Moreover, there are warnings about serious side effects for eszopiclone, including respiratory depression, anaphylactoid symptoms, and drug dependence, whereas no such warning of critical side effects has been released for suvorexant as of today. From these considerations, we suggest that suvorexant is essentially a safe drug, and that its safety can be sustained in combination with other drugs.

Further to its demonstrated safety, suvorexant induces less falling, which is a primary concern of elderly people with insomnia, as well as having less effect on cognitive functions among the elderly. Given the aging society anticipated in Japan, insomnia treatments for the elderly, who tend to experience frequent sleep interruption or early morning waking, poses a challenge [18]. Ramirez et al. [19] have examined the effects of DORAs (with antagonistic action at both orexin receptors 1 and 2) such as suvorexant on motor functions. They observed clear inhibitory effects on motor functions for all drug agents that act on GABA-A receptors and ethanol in a dose-dependent manner. However, no such effects were observed with DORA-12, a back-up compound of suvorexant, even at the maximum dose [19]. Uslaner et al. [20] demonstrated in a study of rats and rhesus monkeys that low dose BZD did not bring about a sleep inducing effect but could still affect memory. They reported that DORA-22, a back-up compound of suvorexant, did not affect memory at a dose that induced a sleep inducing effect [20]. Thus, because DORA has a low risk of inducing falling, and has not been observed to have an effect on memory, suvorexant is considered useful for treatment of insomnia in elderly Japanese people, a population that is predicted to increase in the future.

BZDs are already prescribed for elderly people with insomnia in Japan. Grants-in-Aid for Scientific Research supported by the Ministry of Health, Labour and Welfare has reported that the prescription rate of BZD is on the rise along with the aging population in Japan [21]. Adverse effects, such as falling, bone fractures or reduced cognitive function have been reported following the use of BZD in elderly people. It may therefore be necessary to replace BZD, which have many

drawbacks, with suvorexant, and establishing a method of effective replacement is imperative.

For patients with insomnia who are currently using BZD, we propose the approach of additional administration of suvorexant to secure sufficient duration of sleep, followed by gradual reduction and eventual discontinuation of unnecessary BZD. There are three grounds for taking this approach. First, additional administration of suvorexant to exacerbated insomnia symptoms can prevent the need for further increases in BZD dose. Second, administration of suvorexant reduces the risk of rebound insomnia, which makes it easier to discontinue BZD. Lastly, side effects that carry a large risk in the elderly, such as delirium, falling, or bone fracture [22-25] were not observed in this study. Furthermore, no differences in drug continuation rates were observed in patients with and those without concurrent use of BZD. Therefore, our study findings demonstrated that additional administration of suvorexant to users of BZD is safe. On these grounds, we expect suvorexant to be an effective sleep medication that will ameliorate the problems associated with complex prescriptions for insomnia in Japan where BZD are still in frequent use.

Limitations

Several limitations must be considered in the present study. First, information regarding severity of primary disease, medical history, and life stress was lacking. Second, the criteria for continuous administration of suvorexant differed for each doctor. Third, placebo effects were not considered. Fourth, only side effects reported to the clinician completing the medical record were counted. It is possible that some people suspended treatment in our clinic due to side effects, or that some people continued to take them without noticing side effects, even if such side effects were present. Lastly, our study did not consider drug continuation and side effect rates over the longer term of more than 90 days.

Conclusions

In this study, we examined suvorexant prescription continuation rates over 90 days during the acute psychiatric treatment period. We observed that concurrent use of BZD was found not to be related to withdrawal from suvorexant. We suggest that this drug offers an important method to ensure improvement in insomnia symptoms while reducing the administration of unnecessary drugs. This offers a more effective approach than to defer administration of suvorexant, which may promote exacerbation of the primary disease and reduce quality of life, as well as facilitating continued long-term administration of BZD, simply to avoid concurrent drug use. Future studies that investigate the long-term continuation rate over periods of 6 months to a year are necessary to increase our knowledge of longer-term treatment of insomnia.

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