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The Effect of Recommending Lemborexant as the First-Line Medication for Insomnia on Inpatient Falls

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Abstract

Background: *Falls in hospital inpatients are a common and important issue. Sine γ-aminobutyric acid-A receptor (GABA) agonists are known to be associated with an increased risk of falls, our Committee of Medical Quality Management and Patient Safety recommended lemborexant as the first-line medication for insomnia beginning in October, 2021. This retrospective before-after study was designed to clarify whether this recommendation contributed to a reduction in the inpatient falls rate in our hospitals.*

Methods: *This study was conducted at Yoka Municipal Hospital in Yabu-city, Hyogo, Japan between October 2020 and September 2022. We extracted subjects who were reported to have falls in our hospital's incident report system, which provided records of all falls during the study period. All medications for insomnia were collected from the electronic prescription system in our pharmacy during the study period, and we examined changes in prescriptions for insomnia medications before and after the recommendation. This retrospective before-after study compared the number and rate of inpatients falls before and after the recommendation. Furthermore, we examined the association between the first-line medication for insomnia and falls.*

Results: *The number of prescriptions of GABA agonists and suvorexant significantly deceased after the recommendation, while prescriptions of lemborexant significantly increased. However, this did not reduce the rate of inpatients falls. There was a significant association between suvorexant and falls (odds ratio: 1.41; 95% CI: 1.11~1.79), whereas no significant association was observed between brotizolam, zolpidem or lemborexant and inpatients falls.*

Conclusion*: Our recommendation of lemborexant as the first-line medication for insomnia did not reduce the number or rate of inpatients falls. On the other hands, suvorexant was significantly associated with inpatients falls, whereas brotizolam, zolpidem and lemborexant were not in our study population.*

Keywords: *Fall; Inpatients; Medications; Orexin Receptor Antagonists; Benzodiazepines and Z Drugs.*

Abbreviations

γ-aminobutyric acid (GABA); dual orexin receptor antagonists (DORAs);

INTRODUCTION

Falls in hospital inpatients are one of the most common accidents, with reported rates ranging from 3 to 14 per 1000 occupied bed days [1]. Inpatients fall have a multifactorial etiology and factors that influence the risk of falling include the state of health and drug usage [2,3]. Although γ-aminobutyric acid (GABA)-A receptor agonists such as benzodiazepines are commonly used for insomnia, they are well known to be associated with an increased risk of falls [4-6].

Recently, dual orexin receptor antagonists (DORAs), including suvorexant and lemborexant, have been developed and approved for insomnia [7-9]. The pharmacological mechanism of DORAs differs from that of GABA-A receptor agonists. While GABA-A receptor agonists act as positive allosteric modulators at the GABA-A receptors and augment sleep signaling, DORAs attenuate excessive wakefulness/arousal signaling. So far, there has been no clear evidence demonstrating that DORAs are associated with an increased risk of falls. Therefore, we hypothesized that use of DORAs

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instead of GABA-A receptor agonists may help decrease the rate of falls in hospital inpatients.

In addition, recent clinical researches have documented the superiority of lemborexant [8.10] Thus, the Committee of Medical Quality Management and Patient Safety in our hospital recommended lemborexant, one of the DORAs available in our hospital, as the first-line medication for insomnia beginning in October, 2021. The present study is a retrospective before-after analysis of 24 months of fall data and was designed to clarify whether changes in medication for insomnia contributed to a reduction in the falls rate in our hospitals.

METHODS

This retrospective before-after study was approved by the IRB of Yoka Municipal Hospital (Yoka Municipal Hospital IRB ID: 2022-1; approved date: July 1,2022) and was registered the UMIN Clinical Trial Registry (UMIN 000047974).

This study was conducted at Yoka Municipal Hospital in Yabu-city, Hyogo, Japan. This 350-bed community hospital is located in a rural area where the aging population is more pronounced than in urban areas. The study period was from October 2020 to September 2022. Eligible cases were subjects who were reported to have falls in our hospital's incident reporting system, which provides records of all falls and other types of incidents during the study period. A fall was defined as "an unintended change of position which results in the person coming inadvertently to the ground or other surface lower than the person had been previously" or "a patient reported to the nurse after a fall occurred and the event was documented in the medical record" [11]. The reporting system also includes a free-text description of each fall, and we identified inpatients who suffered bone fractures requiring treatment, including surgery, or permanent harm such as brain damage directly attributed to the fall.

We examined the cumulative number of inpatients falls for each month of the study period and calculated the falls rate as the incident of falls per 1000 occupied bed days, according to a previous report [1]. All medications for insomnia were collected from the electric prescription system in our pharmacy during the study period, and medications administered within 24 hours prior to each fall were recorded.

The Committee of Medical Quality Management and Patient Safety in our hospital recommended lemborexant, one of DORAs, as the first-line medication for insomnia to reduce inpatients falls, starting on October 1, 2021 (Figure 1). Before this recommendation, there was no standardized first-line medication for insomnia. (Figure 1). This study was designed to compare the rate of inpatients falls before and after the recommendation and to examine the effect of this recommendation on inpatient fall rates. Furthermore, we examined the association between the first-line medication for insomnia and falls.

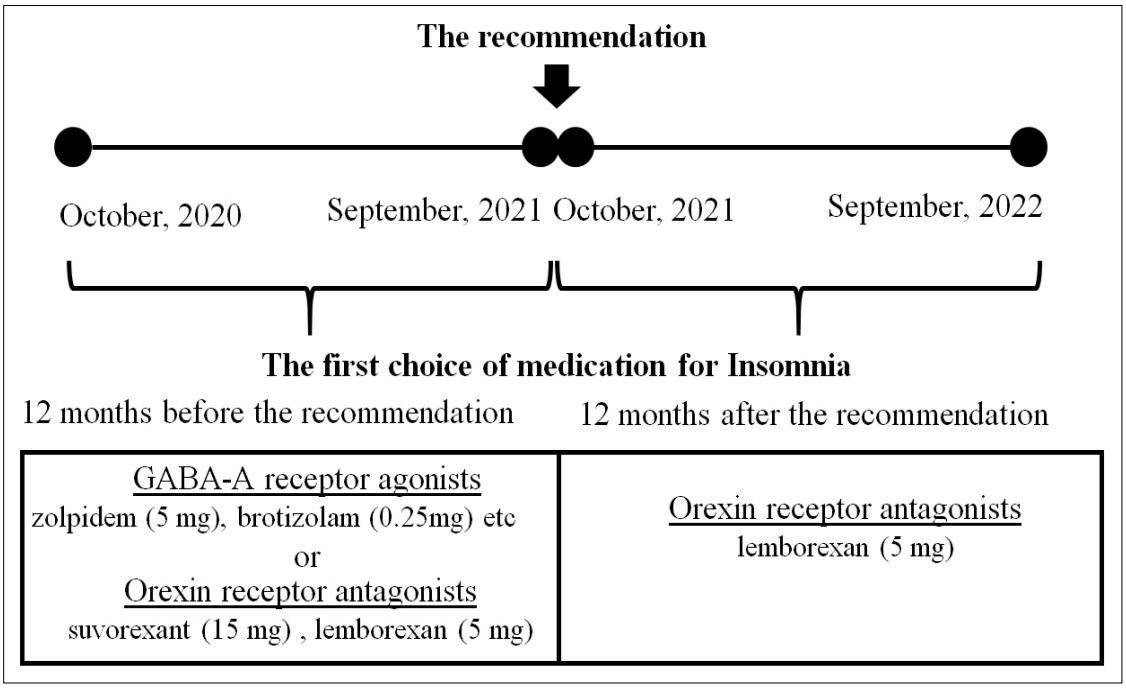

Figure 1. Flowchart illustrating the first-choice medication for insomnia before and after the recommendation.

STATISTICAL ANALYSIS

Data were expressed as means ± SD or as a median and interquartile range, as appropriate. Statistical analysis was performed using SPSS ver. 29 (IBM, Chicago, IL, USA). Comparisons between two groups were analyzed using the $\chi 2$ test, unpaired t test or Mann-Whitney U test, as appropriate. Odd ratios were use as measures of the strength of association between medications for insomnia and inpatients falls. A $P < 0.05$ was considered statistically significant.

RESULTS

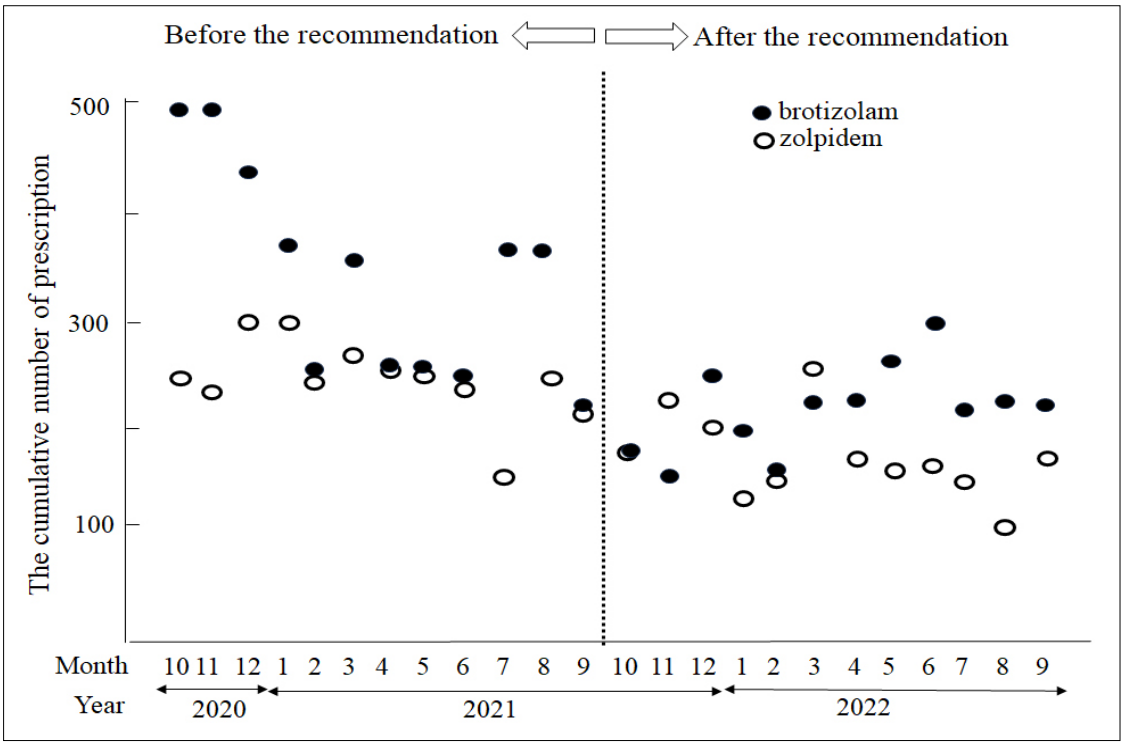

Figure 2. Monthly cumulative number of γ-aminobutyric acid-A receptor agonists (brotizolam and zolpidem) prescribed for insomnia during the study period.

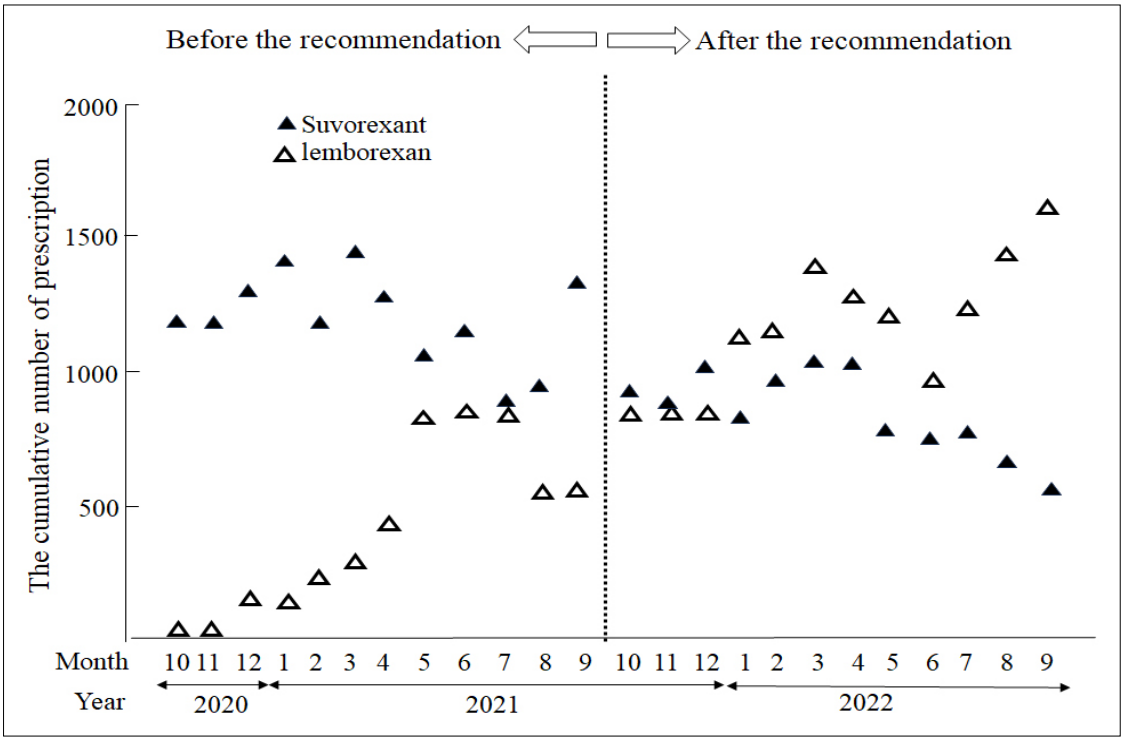

Figure 3. Monthly cumulative number of dual orexin receptor antagonists (suvorexant and lemborexant) prescribed for insomnia during the study period.

Figure 2 and 3 show the changes in the monthly cumulative number of (GABA)-A receptor agonists (brotizolam, and zolpidem) and DORAs (suvorexant and lemborexant), respectively, prescribed for insomnia during the study period. The comparison before and after the recommendation is summarized in Table 1. Prescriptions of GABA-A receptor agonists (brotizolam and zolpidem) significantly decreased after the recommendation (Table 1). Conversely, prescriptions of suvorexant significantly decreased, whereas prescriptions of lemborexant significantly increased (Table 1). As the results, the total number of DORA prescriptions significantly increased (Table 1).

Table 1. The summary of change of monthly cumulative number of medication for insomnia before and after the recommendation.

Medication	Before the recommendation (12)	After the recommendation (12)	P value*
Brotizolam	349.5 (246.75 ~ 385.75)	213.5 (196.25 ~ 225.75)	0.0015
Zolpidem	242 (219.5 ~ 258)	167.5 (147.5 ~ 192)	0.0032
Suvorexant	1169 (1099.5 ~ 1311.5)	833.5 (760.75 ~ 987.5)	0.0005
Lemborexan	401 (167 ~ 615.75)	1154 (954.5 ~ 1315.75)	0.0001
Suvorexant + Lemborexant	1610.5 (1437.25 ~ 1794.75)	1994 (1822.75 ~ 2103.25)	0.0018

Data were expressed as a medianand interquartile range. The number of sample was shown in the parenthesis.

*p value: compared with the value between before and after the recommendation with Mann-Whitney U test

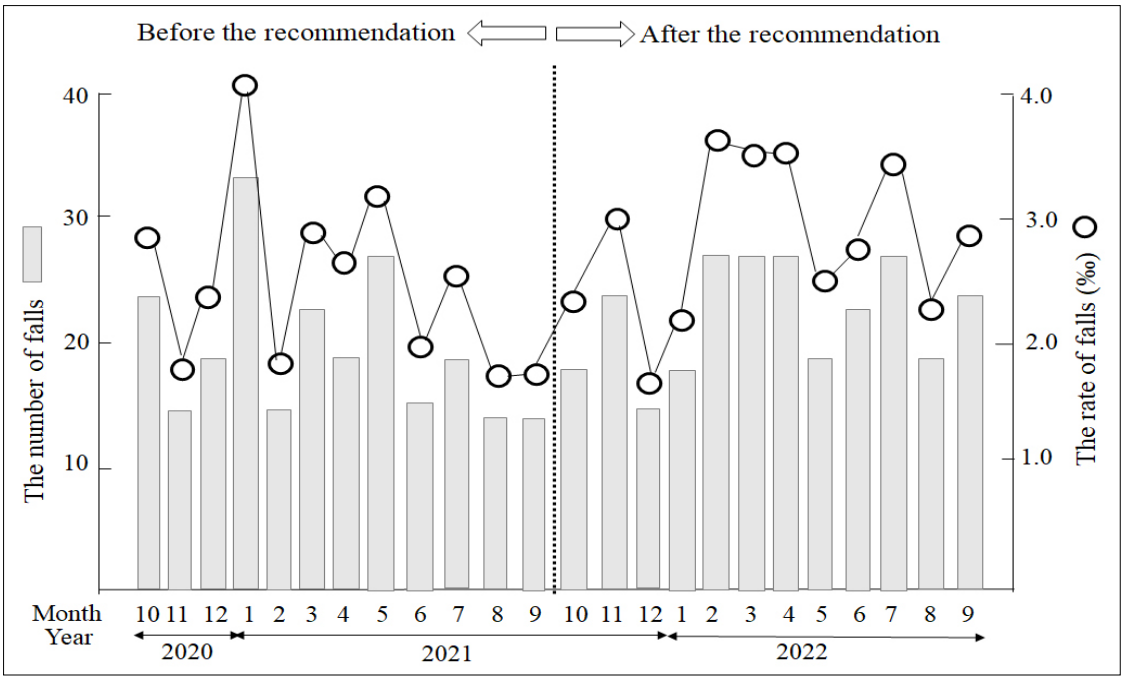

Figure 4. Monthly number of falls and fall rates during the study period. The left axis shows the number of falls, and the right axis shows the fall rates (‰).

Figure 4 shows the number of falls and the rate of falls in each month during the study period, and the comparison before and after the recommendation is summarized in Table 2. The cumulative number of inpatients and inpatients falls during the study period was 186,504 and 481, respectively. Thus, the comprehensive fall rate in our hospital during the study period was calculated as 2.58 ‰. The recommendation affected neither the number of falls nor the fall rate (Table 2). Although the occurrence of severe damage attributed to falls decreased, this difference was not statistically significant (Table 2).

Table 2. The monthly number of falls and the rate of falls and the number of severe damage attributed to the falls before and after the recommendation during the study period.

	Before the recommendation (12)	After the recommendation (12)	P value*
The number of falls	18.8 ± 6.8	21.2 ± 5.0	0.33
The rate of falls** (‰)	2.41 ± 0.72	2.72 ± 0.65	0.26
Severe damage attributed to the fall*** (n)	4[a]	2[b]	0.33

Data are expressed as mean ± SD. The number of sample was shown in the parenthesis.

*p value: compared the value between before and after the recommendation with unpaired t test (the umber of falls, the rate of falls) or χ^2 test (severe damage attributed to the fall)

**The rate of falls was calculated as falls per 1000 occupied bed days in every month.

***inpatients suffering from bone fractures requiring surgery or permanent harm such as brain damage which was directly attributed to the fall.

[a]2 hip fracture and 2 fracture of humerus. [b]2 hip fracture.

Table 3 lists the four medications among patients with and without falls over the 24 months study period. For example, brotizolam prescriptions were 3.33 % in the falls group and 3.54 % in the no-falls group with no significant association between brotizolam and falls (Table 3). Similarly, there was no significant association between zolpidem and falls or between lemborexant and falls (Table 3). In contrast, suvorexant showed a significant association with falls (Table 3).

Table 3. Association between medications for insomnia and falls before and after the recommendation and during the 24 months whole study period.

A. Before the recommendation (October 2020 ~ September 2021)

Medication	Fall (n = 226)	No Fall (n = 92503)	Odds ratio	95 % CI	P value*
Brotizolam	13 (5.75 %)	4016 (4.34 %)	1.34	0.76 ~ 2.36	0.299
Zolpidem	7 (3.097 %)	2867(3.099 %)	0.99	0.47 ~2.12	0.999
Suvorexant	47 (20.80 %)	14169 (15.31 %)	1.45	1.05 ~2.00	0.022
Lemborexan	14 (6.19 %)	5006 (5.41 %)	1.15	0.67 ~ 1.98	0.603

B. After the recommendation (October 2021~ September 2022)

Medication	Fall (n = 255)	No Fall (n = 93520)	Odds ratio	95 % CI	P value*
Brotizolam	3 (1.32 %)	2588 (2.77 %)	0.42	0.13 ~ 1.31	0.122
Zolpidem	5 (1.96 %)	2042 (2.18 %)	0.90	0.37 ~ 2.17	0808
Suvorexant	37 (14.51 %)	10101 (10.80 %)	1.40	0.99 ~ 1.99	0.057
Lemborexan	35 (13.73 %)	13701 (14.65 %)	0.93	0.65 ~ 1.32	0.677

C. Whole study period (October 2020 ~ September 2022)

Medication	Fall (n = 481)	No Fall (n = 186023)	Odds ratio	95 % CI	P value*
Brotizolam	16 (3.33 %)	6604 (3.55 %)	0.93	0.57 ~ 1.54	0.791
Zolpidem	12 (2.50 %)	4904 (2.64 %)	0.94	0.53 ~1.66	0.848
Suvorexant	84 (17.46 %)	24270 (13.05 %)	1.41	1.11 ~1.79	0.004
Lemborexan	49 (10.19 %)	18707 (10.06 %)	1.01	0.75 ~ 1.36	0.924

CI: confidence interval.

Data are expressed as the number of sample with percentage in the parenthesis.

Odds ratio of each medication for insomnia for falls.

*p value for interaction between Falls and No Falls with χ^2 test.

DISCUSSION

Our Committee of Medical Quality Management and Patient Safety recommended prescription of lemborexant as the first-line of medication for insomnia. The main finding of this retrospective before-after study is that the recommendation did not affect the rate of inpatients falls. Another noteworthy finding is that suvorexant was significantly associated with inpatients falls, whereas brotizolam, zolpidem or lemborexant were not.

It is well known that GABA-A receptor agonists, such as benzodiazepines, are associated with an increased risk of falls [4-6]. Thus, we hypothesized that replacing GABA-A receptor agonists with lemborexant, a DORA, might reduce inpatient fall rate. However, the results were unexpected. As shown in Figure 4 and Table 2, the recommendation did not affect the rate of inpatients fall. Therefore, we reviewed our data and considered the reasons for these unexpected results.

Prescriptions of brotizolam and zolpidem, the most commonly used GABA-A receptor agonists in our hospital, significantly deceased after the recommendation (Figure 2, Table 1). Conversely, prescriptions of lemborexant markedly increased, while that of suvorexant significantly decreased (Figure 3, Table 1). As a result, DORA prescriptions (lemborexant + suvorexant) significantly increased (Table 1). Based on these findings, we believe that the recommendation had a certain degree of effect on changing of the prescribing patterns for insomnia. Thus, these findings suggest that our hypothesis- that replacing GABA-A receptor agonists and suvorexant with lemborexant would reduce inpatient falls- may be questionable.

In our data, the number of suvorexant prescription was the highest among insomnia medications at the beginning of the study period (October 2020), (Figure 3). A recent questionnaire-based study in Japan showed that DORAs are the most frequently used insomnia medications [12], so our findings may reflect usual prescribing trends in Japan. Ideally,

prescriptions would have shifted dramatically from GABA-A receptor agonists and suvorexant to lemborexant after the recommendation. However, this was likely not feasible in real clinical practice. Because the recommendation was not mandatory, we could not completely eliminate prescriptions of GABA-A receptor agonists or suvorexant (Table 2). This must be acknowledged as a limitation of our study design.

Although our primary results were disappointing, we observed a strong association between suvorexant and falls during data analysis. Therefore, we examined the association between each insomnia medication and falls before and after the recommendation and across the entire study period (Table 3). An unexpected bonus was that the prevalence of suvorexant was higher in the falls group than that in the non-falls group, with an odds ratio greater than 1.4 and a 95 % confidence interval of 1.11 ~ 1.79, indicating a statistically significant association. In contrast, brotizolam, zolpidem and lemborexant showed no significant association with falls.

Although Suvorexant and lemborexant are classified as DORAs, previous basic research indicates pharmacological differences. Lemborexant exhibits stronger inhibition at orexin 2 receptors than orexin 1 receptors, whereas suvorexant shows similar inhibition at both receptors [13]. Lemborexant also dissociates more rapidly from orexin receptors than suvorexant [13]. Because orexin 2 receptors are primarily responsible for suppressing non-REM sleep onset [14], lemborexant may promote sleep with less risk of residual somnolence. In fact, a recent clinical review of nine studies which examined the potential of lemborexant for residual morning and next-day effects reported a lack of residual morning effects, including somnolence, with lemborexant [10]. On the other hand, another recent comparative clinical study found no definitive difference in adverse events, including somnolence, between lemborexant and suvorexant [15,16]. Thus, while our data suggests a lower fall risk with lemborexant, they should be interpreted with caution.

Inpatient falls have a multifactorial etiology and can be categorized as care-related (e.g., slippery flooring, inadequate lighting), patient-related (e.g., muscle weakness, gait impairment, visual and/or cognitive impairment) or medication-related (e.g., use of certain medications, polypharmacy) [17,18]. Our study focused only on insomnia medication and does not account for all sources of the factors mentioned above, so further research is warranted. We believe that the present findings provide valuable insight for designing future studies comparing the fall risk of suvorexant and Lemborexant.

Our data suggest that brotizolam, zolpidem and lemborexant have similar fall risks. However, GABA-A receptor agonists carry additional concerns, including dependence, abuse, memory impairment and confusion in older patients [19]. Furthermore, because our hospital is located in a rural area where the aging population is more pronounced than in urban areas, many inpatients may have additional fall risk factors such as impaired physical function, reduced muscle mass and decreased strength. Considering these circumstances, we recommend lemborexant as the first-line insomnia medication in our population.

There are some limitations in this study. First, all data were obtained from a single community hospital in a rural area with a markedly aging population, which may limit generalizability. Second, the significant association between suvorexant and falls depends on the statistical analysis, so the clinical significance of our data would be interpreted with caution. Finally, the retrospective nature of this study introduces potential bias, as inpatient management was not standardized, and other risk factors for falls may have influenced the results.

CONCLUSION

Our recommendation that Lemborexant -not GABA-A receptor agonists or suvorexant- is used as the first-line medication for insomnia did not affect the number or rate of inpatient falls. However, suvorexant showed a significant association with inpatients falls, whereas brotizolam, zolpidem and lemborexant did not.

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Competing Interests

Yuko Takahashi received speaker's honoraria from Eisai Co. Ltd. No other conflicts of interest were declared by the remaining authors.

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Author Contributions

YT made the recommendation for insomnia, performed data extraction and analysis, discussed the data and wrote the manuscript. AU performed data extraction and data analysis. ST performed data extraction and discussed the data. YO and MF advised to make the recommendation and discussed the data. YH made the recommendation for insomnia, supervised the study, discussed the data and revised the manuscript.

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