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SHORT REPORT

The Administration of Lemborexant at Admission is Not Associated with Inpatient Falls: A Multicenter Retrospective Observational Study

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Purpose: There has been no large-scale investigation into the association between the use of lemborexant, suvorexant, and ramelteon and falls in a large population. This study, serving as a pilot investigation, was aimed at examining the relationship between inpatient falls and various prescribed hypnotic medications at admission.

Patients and Methods: This study was a sub-analysis of a multicenter retrospective observational study conducted over a period of 3 years. The target population comprised patients aged 20 years or above admitted to eight hospitals, including chronic care, acute care, and tertiary hospitals. We extracted data on the types of hypnotic medications prescribed at admission, including lemborexant, suvorexant, ramelteon, benzodiazepines, Z-drugs, and other hypnotics; the occurrence of inpatient falls during the hospital stay; and patients' background information. To determine the outcome of inpatient falls, items with low collinearity were selected and included as covariates in a forced-entry binary logistic regression analysis.

Results: Overall, 150,278 patients were included in the analysis, among whom 3,458 experienced falls. The median age of the entire cohort was 70 years, with men constituting 53.1%. Binary logistic regression analysis revealed that the prescription of lemborexant, suvorexant, and ramelteon at admission was not significantly associated with inpatient falls.

Conclusion: The administration of lemborexant, suvorexant, and ramelteon at admission may not be associated with inpatient falls.

Keywords: lemborexant, hypnotics, in-hospital falls, risk factor

Introduction

In-hospital falls present significant challenges, contributing to societal burdens such as increased healthcare costs and physical and psychological burdens on patients,[1] including physical sequelae and fear of falls.[2,3] Hypnotic medications are recognized risk factors for falls,[4] and their use often increases during hospitalization because of changes in both the environment and the patient's condition, leading to insomnia.[5] While benzodiazepine hypnotics (BZs) have been previously reported to be associated with falls,[6] in recent years, new hypnotic medications, such as lemborexant, suvorexant, and ramelteon, have become available. However, there is a dearth of multicenter studies examining the association between these novel hypnotic medications and falls. Definitive evidence of the association between suvorexant and falls has not been shown, even in studies with small populations.[7,8] Remarkably, the relationship between lemborexant and falls has been scarcely investigated, with only few single-center studies addressing this issue.[9] This study, serving as a pilot investigation, was aimed at examining the association between inpatient falls and various hypnotic medications by using multicenter data.

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Materials and Methods

This study was a sub-analysis of an unpublished multicenter retrospective study conducted from April 1, 2018, to March 31, 2021, targeting patients aged 20 years or above admitted to eight hospitals, including chronic care, acute care, and tertiary hospitals. Patient data, including background information such as age,[10,11] sex, underlying conditions, and the occurrence of inpatient falls, were extracted from their medical records. We collected prescription data from drug pharmacy records for medications with the first three digits of the Ministry of Health, Labour and Welfare Drug Code (YJ Code) 112, suvorexant, lemborexant, and ramelteon, up to the day following admission. Subsequently, we categorized these medications into the following groups: BZs, Z-drugs, suvorexant, lemborexant, ramelteon, and other hypnotics. The collected data on underlying conditions included those pertaining to emergency admission,[10] Bedriddenness Rank,[10,12] Cognitive Function Score,[10,13] activities of daily living (ability to eat, transferring, groom, use the toilet, bathe, walk independently on ground level, climb stairs, change clothes, maintain bowel and bladder self-control),[10] emergency transportation,[14] referral letter,[14] care level,[15] consciousness disturbance, admitting department,[10] dysphagia, urinary frequency,[16] diabetes mellitus (ICD-10: E10-14),[17] history of stroke (I60.0-I64, I69),[18,19] lower limb paralysis (G81.0, G81.1, G81.9, G83.1, G82.1), Parkinson's syndrome (G20, G21),[11] ophthalmic diseases (H25, H26, H28.1, H40 (other than 40.7), H42, Q15.0), visual impairment (assessment through self-report),[20] alcoholism (F10.0–10.9), surgical operations during hospital stay,[15] rehabilitation,[15] antipsychotic medication use,[13] independence in taking prescription drugs, use of mobility aids,[21] and history of falls before admission.[11,12] The Bedriddenness Rank and the Cognitive Function Score are public activities of daily living scales developed by Japan's Ministry of Health, Labour and Welfare. The Bedriddenness Rank has five major classes (normal, J, A, B, and C), and the Cognitive Function Score has six (normal, I, II, III, IV, and M).[20] In analyzing inpatient falls as the outcome, all categories of hypnotic medications and factors collected, ensuring a Spearman correlation coefficient of <0.5 for low collinearity among all variables, were included. For highly collinear pairs, one of the variables was selected as a covariate, and all variables were forced into a binary logistic regression analysis. The significance level was set at <0.05. This study adheres to the principles outlined in the Declaration of Helsinki, as well as the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology. The study was approved by the Ethics Committee of Saga University Hospital (approval ID: 2023–08-SC-07).

Results

Overall, 150,278 patients aged 20 years or older admitted during the study period, with 3,458 cases of falls, were included. The median age was 70 years, and 53.1% were men (Table 1). Among these inpatients, 390 (0.3%), 2,777 (1.8%), 2,130 (1.4%), 13,271 (8.8%), and 5,634 (3.7%) were prescribed lemborexant, suvorexant, ramelteon, BZs, and Z-drugs, respectively. Hospital, age, sex, emergency admission, Bedriddenness Rank (normal, J, A, B, or C), Cognitive Function Score (normal, I, II, III, IV, or M), emergency transportation, referral letter, care level, consciousness disturbance, use of walking aids, admitting department, independence of ground-level walking (independent or assisted), dysphagia, urinary frequency, diabetes mellitus, history of stroke, lower limb paralysis, Parkinson's syndrome, ophthalmic diseases, visual impairment,

Table 1 Characteristics of Patients

Variable, Category	All Patients n = 150,278	Fall Group n = 3,458	Non-Fall Group n = 146,820
Age, years	70 (58–79)	77 (69–84)	70 (58–79)
Sex, Men	79,781 (53.1)	2,016 (58.3)	77,765 (53.0)
Benzodiazepine hypnotics, Using (Not using)	13,271 (8.8)	429 (12.4)	12,842 (8.7)
Z-drugs, Using (Not using)	5,634 (3.7)	218 (6.3)	5,416 (3.7)
Ramelteon, Using (Not using)	2,130 (1.4)	130 (3.8)	2,000 (1.4)
Suvorexant, Using (Not using)	2,777 (1.8)	150 (4.3)	2,627 (1.8)
Lemborexant, Using (Not using)	390 (0.3)	25 (0.7)	365 (0.2)
Others, Using (Not using)	102 (0.1)	4 (0.1)	98 (0.1)

(*Continued*)

Table 1 (Continued).

Variable, Category	All Patients n = 150,278	Fall Group n = 3,458	Non-Fall Group n = 146,820
Bedriddenness rank, Normal	5,063 (3.4)	44 (1.3)	5,019 (3.4)
Bedriddenness rank, J	61,599 (41.0)	667 (19.3)	60,932 (41.5)
Bedriddenness rank, A	25,363 (16.9)	844 (24.4)	24,519 (16.7)
Bedriddenness rank, B	13,507 (9.0)	743 (21.5)	12,764 (8.7)
Bedriddenness rank, C	25,330 (16.9)	858 (24.8)	24,472 (16.7)
Bedriddenness rank, missing	19,416 (12.9)	302 (8.7)	19,114 (13.0)
Cognitive function score, Normal	114,096 (75.9)	2,252 (65.1)	111,844 (76.2)
Cognitive function score, I	6,750 (4.5)	339 (9.8)	6,411 (4.4)
Cognitive function score, II	4,065 (2.7)	260 (7.5)	3,805 (2.6)
Cognitive function score, III	4,748 (3.2)	355 (10.3)	4,393 (3.0)
Cognitive function score, IV	1,819 (1.2)	94 (2.7)	1,725 (1.2)
Cognitive function score, M	352 (0.2)	23 (0.7)	329 (0.2)
Cognitive function score, missing	18,448 (12.3)	135 (3.9)	18,313 (12.5)

Notes: Continuous and categorical variables are shown as median value (interquartile range) and number (percent). Bedriddenness ranks: J, independence/autonomy; A, house-bound; B, chair-bound; C, bed-bound. Cognitive function scores: I, almost independent in daily living with only slight cognitive impairment; II, independent with slight difficulty in daily living or communication under careful overseeing; III, dependent in daily living or communication; IV, dependent in daily living or communication, and requires constant care; M, severe psychological symptoms, troubled behaviors or severe physical disorders requiring specialized medical service.

alcoholism, surgical operation during hospital stay, rehabilitation, antipsychotic medication, and history of falls had Spearman correlation coefficients of <0.5 each. Logistic regression analysis was performed for these factors and the six hypnotic medications (lemborexant, suvorexant, ramelteon, BZs, Z-drugs, and others) totaling 32 items. We found that the prescription of lemborexant ($p = 0.431$), suvorexant ($p = 0.167$), and ramelteon ($p = 0.412$) at admission was not significantly associated with in-hospital falls. In contrast, the prescription of BZs and Z-drugs at admission had odds ratios of 1.26 ($p < 0.001$) and 1.29 ($p = 0.001$), respectively, indicating a significant association with falls (Table 2).

Discussion

In this study, BZs and Z-drugs were found to be significantly associated with in-hospital falls. However, new hypnotic medications prescribed at admission, namely lemborexant, suvorexant, and ramelteon, were not significantly associated with falls in this multicenter study.

The association between novel hypnotic medications and falls has thus far been reported only in small-scale studies.[8,22,23] In a study by Sogawa et al investigating the relationship between lemborexant and falls in a single-center study, lemborexant reduced the risk of falls.[9] Furthermore, the association of suvorexant with falls yielded

Table 2 Results of Multivariable Logistic Regression Analysis (Extracted)

Variable, Category (Reference)	OR	95% CI		p value†
Age	1.012	1.009	1.015	< 0.001
Sex, Men (Women)	1.273	1.184	1.368	< 0.001
Benzodiazepine hypnotics, Using (Not using)	1.255	1.118	1.409	< 0.001
Z-drugs, Using (Not using)	1.293	1.118	1.496	0.001
Ramelteon, Using (Not using)	1.087	0.891	1.326	0.412
Suvorexant, Using (Not using)	1.139	0.947	1.369	0.167
Lemborexant, Using (Not using)	1.188	0.774	1.825	0.431
Others, Using (Not using)	1.261	0.452	3.522	0.658

Note: †p values for Wald test.
Abbreviations: OR, odds ratio, 95% CI: 95% confidence interval.

different results from previous studies.[7,8] This discrepancy may be attributed to variations in analytical methods and the studies being focused on single-center or small-scale facilities. However, the present study, conducted across multiple facilities, did not reveal a significant association between lemborexant, ramelteon, and suvorexant and falls. BZs and Z-drugs exhibit pharmacological actions related to the gamma-aminobutyric acid (GABA) receptors, contributing to reported effects such as sedation and muscle relaxation.[24] These medications are also known to be associated with various side effects, including delirium, orthostatic hypotension, dizziness, motor impairment such as muscle weakness and extrapyramidal symptoms, and visual impairment,[25] and were significantly associated with falls in this study; this finding was similar to those of previous studies.[6,10] However, unlike BZs and Z-drugs, the new hypnotic medications, lemborexant, suvorexant, and ramelteon, do not interact with GABA receptors.[24] Ramelteon utilizes melatonin, which controls circadian rhythms through G protein–coupled receptors (MT1/MT2) and lemborexant and suvorexant utilize orexin antagonists through orexin receptors to regulate sleep cycles.[24] These novel hypnotic medications, unlike BZs and Z-drugs, are less likely to induce sedation or muscle relaxation, pharmacologically minimizing the risk of falls and suggesting a potential lack of association with falls.[24] Additionally, lemborexant, suvorexant, and ramelteon have been reported to have preventive effects against the onset of delirium.[26,27] Because Japan is a leading aged society globally and the median age of our study population was 70 years, falls in older individuals can be influenced by factors such as delirium,[28] making it plausible that the new hypnotic medications were not significantly associated with falls owing to their potential inhibitory effects against delirium onset.

Limitations

The present study was a pilot and retrospective observational study. Data collection regarding hypnotic medications was based on their prescription status only at admission; thus, the study lacked adjustments for medications either added or discontinued during hospitalization. This study was conducted in hospitals across various prefectures, with six out of eight facilities located in rural prefectures in Japan. The majority of the population consisted of inpatients from acute care or tertiary hospitals, potentially introducing selection bias. Additionally, due to the unavailability of data on fall prevention measures, the effect of interventions for fall prevention could not be assessed.

Conclusion

The administration of lemborexant, suvorexant, and ramelteon at admission may not be associated with in-hospital falls. Because their pharmacological actions are distinct from those of the well-established fall-related agents such as BZs and Z-drugs, these medications may not induce sedation and muscle relaxation, which contribute to the risk of falls. Furthermore, the potential of these drugs to prevent delirium might be related to lower fall risks. Further research is necessary to elucidate the association between hypnotic medications and in-hospital falls, considering factors such as the prescription history of hypnotic medications after admission, the time of the most recent ingestion of hypnotic medications before a fall, and the timing of the fall itself.

Abbreviations

BZs, benzodiazepines GABA, gamma-aminobutyric acid.

Data Sharing Statement

The datasets generated and analyzed during the current study are available in the UMIN-ICDR repository (https://center6.umin.ac.jp/cgi-bin/icdr_e/ctr_view.cgi?recptno=R000050831).

Ethics Approval and Informed Consent

This study conforms to Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology. The study was approved by the Ethics Committee of Saga University Hospital (approval ID: 2023-08-SC-07). We obtained consent from all patients by using the hospital's comprehensive agreement method, and patients'

anonymity was protected. We disclosed study information on the hospital's website and allowed patients to opt out of participation.

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Author Contributions

All authors made a significant contribution to the work reported with respect to the conception, study design, execution, acquisition of data, analysis, and interpretation. All authors participated in drafting, revising, or critically reviewing the article and approved the final version submitted for publication. All the authors have agreed to the journal submission and agree to be accountable for all aspects of the work.

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