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Hospitalized patients on orexin receptor antagonists have a lower risk of falls

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Abstract

Falls and fall-related injuries remain a major safety concern in many hospitals and nursing homes. Although many studies have examined the relationship between accidents and sedating medications, further analysis is needed of the association between falls and individual hypnotics. The aim of this study was to clarify the association between hypnotics and the risk of falls in hospital. The impact of hypnotics on fall events was retrospectively evaluated in patients aged 20 years or older who were admitted to Gunma University Hospital between January 2013 and March 2022. Logistic regression analysis was performed with age, sex, and drug prescription status as the independent variables and fall events as the dependent variable. Of the 54,019 patients included in the study, 1,460 experienced a fall during hospitalization (incidence, 2.7%). The hypnotics prescribed included orexin receptor antagonists, melatonin receptor agonists, and benzodiazepine receptor agonists. Logistic regression analysis showed that age (odds ratio [OR] 1.04), male sex (OR 1.14), estazolam (OR 2.99), flunitrazepam (OR 2.34), brotizolam (OR 1.65), diazepam (OR 3.34), lorazepam (OR 2.93), alprazolam (OR 1.91), ethyl loflazepate (OR 2.81), zolpidem (OR 1.40), eszopiclone (OR 1.87), clonazepam (OR 1.94), and ramelteon (OR 2.15) independently contributed to falls. Short-acting benzodiazepine receptor agonists tended to have smaller ORs for fall risk. Orexin receptor antagonists were not associated with falls. Therefore, orexin receptor antagonists and short-acting benzodiazepine receptor agonists are likely safer than intermediate-acting and long-acting benzodiazepines.

Keywords: fall risk, hypnotics, acute care hospitals

1. Introductio

Insomnia is a common problem that affects about 10% of adults [1]. Benzodiazepine receptor agonists have long been widely used as a treatment option. However, benzodiazepines have some well-known disadvantages, including the potential for dependence and increased risk of staggering and falls because of their

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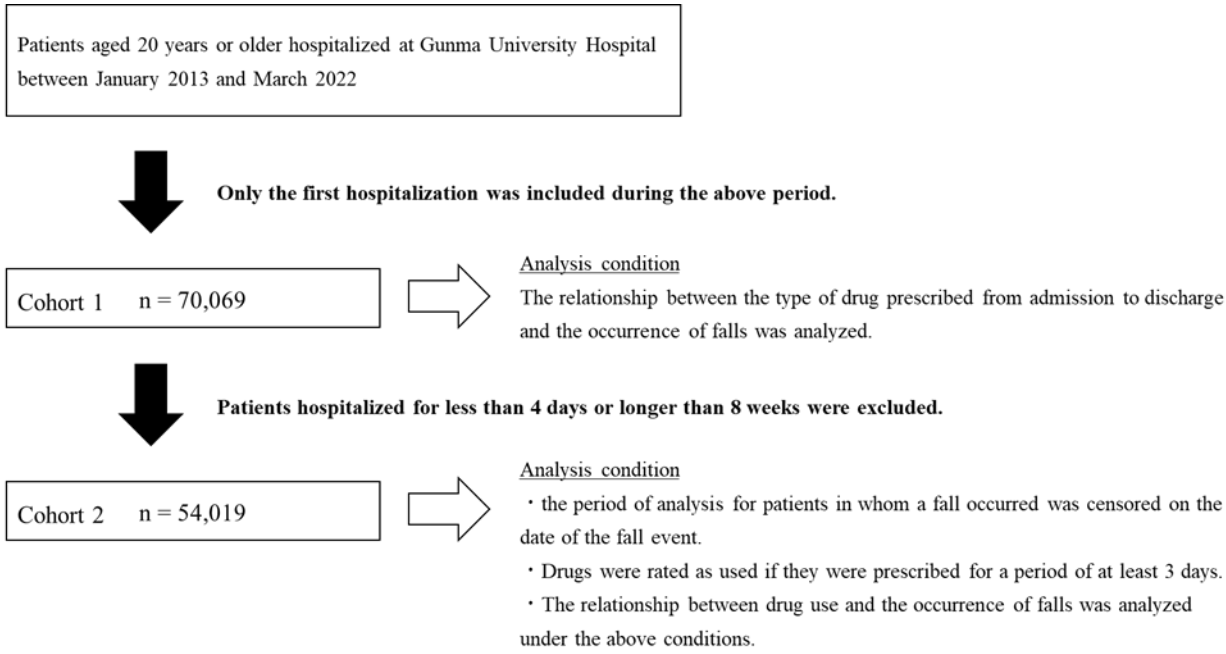
muscle-relaxant effects [2–7]. Falls are a serious clinical problem they occur more frequently in the elderly [8] and are associated with fractures, which lead to prolonged hospitalization, decreased quality of life, and poor prognosis [9–11]. Therefore, falls are a major problem in clinical practice. In a retrospective study of 3,683 patients hospitalized during the fourth quarter of 2007, we found an association between falls and medication and concluded that hypnotics increase the risk of falls but that the actual fall risk significantly depends on the type of hypnotic administered [7]. Three more recently published studies have also investigated the effect of hypnotics on the risk of falls [12–14], but the effect of individual hypnotics on the risk of falls is not yet clear. The lack of progress in understanding the effect of each type of hypnotic on the risk of falls can be attributed to insufficient case numbers and variations in the characteristics of target diseases. A large number of cases under general conditions is required in order to accurately assess the impact of hypnotics on the risk of falls. Recently, orexin receptor antagonists and melatonin receptor agonists have become available for the treatment of insomnia. Unlike benzodiazepine receptor agonists, these drugs show less potential for dependence and have minimal effects on motor function [15–17]. Thus, the fall risk is considered negligible. However, the impact of these medications on the risk of falls varies from study to study and remains controversial [12,18–20]. One reason for the inconsistent findings of these studies is that various benzodiazepine receptor agonists are categorized into one group as "benzodiazepines" when investigating new hypnotics. Our previous study showed that the effect of the various benzodiazepine receptor agonists on the risk of falls varies widely. Therefore, each hypnotic should be evaluated individually when assessing the risk of falls. In this study, we investigated the impact of different types of hypnotics on the risk of falls in all patients admitted to Gunma University Hospital over a 10-year period.

2. Methods

2.1 Patient cohort

All patients over 20 years of age who were hospitalized at Gunma University Hospital between January 2013 and March 2022 were included in the study. Only the first hospitalization was included for patients who were hospitalized on multiple occasions during the study period (cohort 1). Information on all medications administered during the first hospitalization was analyzed.

A second group of patients (cohort 2) was then created with addition of the following conditions to control for patient background factors. First, the period of analysis for patients in whom a fall occurred was censored on the date of the fall event in order to exclude hypnotics taken after the fall occurred. Patients hospitalized for less than 4 days or longer than 8 weeks were excluded to control for variations in medical conditions (e.g., patients who were hospitalized for examination only and those who were bedridden). Finally, patients who had a single prescription of a hypnotic for fewer than 2 days before surgery were excluded.(fig. 1).



2.2 Study design

The relationship between the drugs prescribed and occurrence of falls during the study period was investigated in both study cohorts. Patients who met the study eligibility criteria were examined for age, sex, history of prescriptions for hypnotics, and history of falls. Inpatient falls are registered via incident reports submitted by medical staff. Falls were evaluated according to a previous report by Gibson [21], and medical charts were reviewed to obtain clinical data. All drugs prescribed to the patients during their hospital stay were extracted electronically from hospital charts. The drugs analyzed were those classified as hypnotics according to the therapeutic category of drugs defined by the Japanese Ministry of Health, Labour and Welfare. Thirty-three hypnotics used during the study period were included (estazolam, flurazepam, nitrazepam, haloxazolam, triazolam, flunitrazepam, brotizolam, lormetazepam, oxazolam, cloxazolam, clorazepate dipotassium, diazepam, fludiazepam, bromazepam, medazepam, lorazepam, alprazolam, flutazolam, mexazolam, tofisopam, chlordiazepoxide, ethyl loflazepate, quazepam, midazolam, rilmazafone, zopiclone, tandospirone, zolpidem, eszopiclone, clonazepam, ramelteon, suvorexant, and lemborexant).

The study was approved by the Gunma University Ethics Review Committee for Medical Research Involving Human Subjects (study number HS2020-154).

2.3 Statistical analysis

Categorical variables, including sex and prescriptions for hypnotics, were analyzed for their association with history of falls using the chi-squared test. As a continuous variable, age was analyzed for its association with history of falls using the *t*-test. Multivariate logistic regression analysis was performed for risk factors for falls that had a p value of <0.1 in univariate analysis (age, sex, and hypnotic) for hypnotics prescribed to at least 100 patients. All statistical analyses were performed using the IBM SPSS Statistics 28 software package (IBM Corp., Armonk, NY, USA). A p value of <0.05 was considered statistically significant.

3. Results

3.1 Cohort 1

In total, 2,007 of the 70,069 patients in cohort 1 had a fall during their hospital stay, giving a fall rate of 2.9%. After exclusion of 17 drugs for which there were fewer than

100 prescriptions (flurazepam, haloxazolam, lormetazepam, oxazolam, cloxazolam, clorazepate dipotassium, fludiazepam, bromazepam, medazepam, flutazolam, mexazolam, tofisopam, chlordiazepoxide, quazepam, rilmazafone, zopiclone, and tandospirone), univariate analysis showed that age, sex, and 16 drugs (estazolam, nitrazepam, triazolam, flunitrazepam, brotizolam, diazepam, lorazepam, alprazolam, ethyl loflazepate, midazolam, zolpidem, eszopiclone, clonazepam, ramelteon, suvorexant, and lemborexant) were significantly associated with falls (Table 1).

Variable	All inpatients	Falls	Non-falls	*p* value
Sex				
Male	36055	1110	34945	<0.001
Female	34014	879	33135	
Total	70069	1989	68080	<0.001
age	61.7 ±17.4	69.9 ±14.3	61.5 ±17.5	<0.001
Hypnotics	23432	1114	22318	<0.001
Estazolam	161	16	145	<0.001
Nitrazepam	225	16	209	<0.001
Triazolam	613	32	581	<0.001
Flunitrazepam	567	43	524	<0.001
Brotizolam	4292	289	4003	<0.001
Diazepam	1788	94	1694	<0.001
Lorazepam	355	37	318	<0.001
Alprazolam	372	24	348	<0.001
Ethyl Loflazepate	163	14	149	<0.001
Midazolam	2472	107	2365	<0.001
Zolpidem	12002	399	11603	<0.001
Eszopiclone	612	58	554	<0.001
Clonazepam	296	26	270	<0.001
Ramelteon	833	94	739	<0.001
Suvorexant	812	85	727	<0.001
Lemborexant	709	43	666	<0.001

Table 1. Relationship between type of hypnotic prescribed and risk of falls in study cohort 1

Multivariate analysis showed that all these factors independently contributed to falls (Table 2).

Variable	Multivariate adjusted		*p* value
	OR	(95 % CI)	
Sex	0.85	(0.77-0.93)	<0.001
Age	1.03	(1.03-1.04)	<0.001
Hypnotics			
Estazolam	3.54	(2.09-5.99)	<0.001
Nitrazepam	2.35	(1.40-3.96)	0.001
Triazolam	1.57	(1.10-2.26)	0.014
Flunitrazepam	3.08	(2.24-4.25)	<0.001
Brotizolam	2.75	(2.41-3.14)	<0.001
Diazepam	2.27	(1.83-2.82	<0.001
Lorazepam	4.27	(3.00-6.09)	<0.001
Alprazolam	2.41	(1.58-3.68)	<0.001
Ethyl Loflazepate	3.21	(1.83-5.63)	<0.001
Midazolam	1.60	(1.31-1.96)	<0.001
Zolpidem	1.65	(1.47-1.86)	<0.001
Eszopiclone	3.34	(2.52-4.42)	<0.001
Clonazepam	3.27	(2.16-4.96)	<0.001
Ramelteon	3.24	(2.58-4.07)	<0.001
Suvorexant	3.24	(2.55-4.11)	<0.001
Lemborexant	2.35	(1.71-3.22)	<0.001

Table 2. Risk factors for falls identified by logistic regression analysis in study cohort 1

3.2 Cohort 2

In cohort 2, 1,460 of the 54,019 patients enrolled had a fall during hospitalization, giving a fall rate of 2.7%. Univariate analysis after exclusion of 18 agents with fewer than 100 prescriptions (flurazepam, haloxazolam, lormetazepam, oxazolam, cloxazolam, clorazepate dipotassium, fludiazepam, bromazepam, medazepam, flutazolam, mexazolam, tofisopam, chlordiazepoxide, quazepam, midazolam, rilmazafone, zopiclone and tandospirone) showed that age, sex, and 14 hypnotics (estazolam, nitrazepam, flunitrazepam, brotizolam, diazepam, lorazepam, alprazolam, ethyl loflazepate, zolpidem, eszopiclone, clonazepam, ramelteon, suvorexant, and lemborexant) were significantly associated with falls (Table 3).

Variable	All inpatients	Falls	Non-falls	*p* value
Sex				
Male	26964	804	26160	<0.001
Female	27055	656	26399	
Total	54019	1460	52559	
age	61.7±17.2	70.2 ±14.2	61.5 ±17.2	<0.001
Hypnotics	18761	599	18162	<0.001
Estazolam	117	10	107	<0.001
Nitrazepam	165	9	156	0.029
Triazolam	444	15	429	0.378
Flunitrazepam	190	13	177	<0.001
Brotizolam	2955	134	2821	<0.001
Diazepam	270	23	247	<0.001
Lorazepam	224	16	208	<0.001
Alprazolam	269	14	255	0.011
Ethyl Loflazepate	106	7	99	0.013
Zolpidem	4560	160	4400	<0.001
Eszopiclone	431	23	408	0.001
Clonazepam	202	10	192	0.048
Ramelteon	581	40	541	<0.001
Suvorexant	585	29	556	0.001
Lemborexant	279	14	265	0.017

Multivariate analysis of these factors showed that age, sex, estazolam, flunitrazepam, brotizolam, diazepam, lorazepam, alprazolam, ethyl loflazepate, zolpidem, eszopiclone, clonazepam, and

ramelteon independently contributed to falls (Table 4).

Variable	Multivariate adjusted		*p* value
	OR	(95 % CI)	
Sex	0.88	(0.79-0.97)	0.014
Age	1.04	(1.03-1.04)	＜0.001
Hypnotics			
Estazolam	2.99	(1.55-5.76)	0.001
	2.34	(1.32-4.14)	0.004
Flunitrazepam			
Brotizolam	1.65	(1.38-1.99)	＜0.001
Diazepam	3.43	(2.22-5.31)	＜0.001
Lorazepam	2.93	(1.74-4.93)	＜0.001
Alprazolam	1.91	(1.11-3.30)	0.020
Ethyl	2.81	(1.29-6.12)	0.009
Loflazepate			
Zolpidem	1.40	(1.18-1.65)	＜0.001
Eszopiclone	1.87	(1.22-2.88)	0.004
Clonazepam	1.94	(1.02-3.70)	0.043
Ramelteon	2.15	(1.55-2.99)	＜0.001

Table 4. Risk factors for falls identified by logistic regression analysis in study cohort 2

4. Discussion

In this study, we retrospectively evaluated the relationship between medications prescribed and occurrence of falls in all patients hospitalized at our facility over a 10-year period. As in previous studies [7,12–14,22], we found that use of medications, including many benzodiazepine receptor agonists, was associated with falls in cohort 1 (Tables 1 and 2). However, the previous studies had some drawbacks, including the fact that hypnotics prescribed after a fall were also evaluated as a risk factor for falls. Furthermore, some of the patients included in the analysis had little risk of falling, such as those who had been in hospital for more than one year and were inactive and those who had been hospitalized for only 2 days for examination purposes. Therefore, in the present study, we changed the analysis period to focus on patients who experienced falls from hospital admission to the first fall occurrence. We also limited the length of hospitalization to 4 days or more and 8 weeks or less for the patients in cohort 2. Our findings were consistent with those previously reported, namely, that many benzodiazepines influenced the risk of falls. An exception was triazolam, which is rarely prescribed for the first time during admission to an acute care hospital such as ours. Many patients had been prescribed triazolam before recruitment into the study and were accustomed to taking it, which may have masked their actual risk of falls. Therefore, in order to assess the impact of these drugs on the risk of falls, it is necessary to examine patient factors in detail and include the time interval since the initial prescription. Another finding in our study was that the melatonin receptor

agonist ramelteon increased the risk of falls.

In contrast, we found that prescriptions for the orexin receptor antagonists suvorexant and lemborexant had no impact on the fall risk, similar to the reports by Torii *et al*. and Sogawa *et al* [19–20]. Previous studies of the impact of orexin receptor antagonists on falls have yielded inconsistent results [12,18–20], likely in part because of inclusion of patients on short-term medications or those who were long-stay patients. However, the most significant factor is thought to be the influence of other benzodiazepines. In our cohort 2, 144 (24.6%) of the 585 patients taking suvorexant and 34 (12.2%) of the 279 taking lemborexant had a history of prescriptions for benzodiazepines. Moreover, of the 18,761 patients who were prescribed any hypnotics, 1,339 (7.1%) were prescribed two or more hypnotics. These findings suggest that orexin receptor antagonists were prescribed more often than other hypnotics and that factors related to other drugs may have played a significant role in the risk of falls. In particular, other medications may have contributed significantly to the effect of orexin receptor antagonists on the risk of falls. We did not group benzodiazepines in this study and instead analyzed them individually, which adjusted for the effects of concomitant medications and allowed for an accurate assessment of the impact of orexin receptor antagonists on the risk of falls.

This study has some limitations, including failure to control for the effects of medications other than hypnotics that may impact falls, to evaluate the effects of medications that interact with hypnotics, to determine the dosages at which each medication was administered, and to investigate each patient's disease status and therapeutic interventions in detail. These limitations are largely the result of the limited number of factors that can be incorporated simultaneously when conducting a multivariate analysis. Further studies are needed to confirm our present findings and investigate the relevance of other potential risk factors in more detail.

5. Conclusions

This study retrospectively investigated the effect of hypnotics on the risk of falls in patients hospitalized over a 10-year period. We found that short-acting benzodiazepines, even though relatively safe, were still associated with a significantly increased risk of falls. We also found that melatonin receptor antagonists increased the risk of falls but that orexin receptor antagonists did not. To our knowledge, this is the first study to use big data to determine the impact of individual hypnotics on the risk of falls. Considering our relatively large sample size and the fact that patient background characteristics were controlled to some extent, including adjustment for the number of hospital days, we believe that our results are highly reliable. Therefore, an orexin receptor antagonist is recommended when the risk of falls is the primary consideration. Furthermore, when using benzodiazepines, even those that are short-acting and considered to have a relatively low risk of falls, the patient's risk factors should be carefully evaluated and adequate countermeasures taken as necessary to prevent falls.

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