

MICRO REPORT

Risk assessment of accidental falls in patients taking trazodone, quetiapine, or risperidone for insomnia: A single-center, case-control study

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Abstract

Aim: No consensus has been reached on the association between the risk of falls and antipsychotic and antidepressant drug use. In this study, we evaluated the risk of falls with trazodone, risperidone, and quetiapine, which are recommended for use at Kanazawa Medical University Hospital.

Methods: We reviewed all patients who were admitted to Kanazawa Medical University Hospital between January 1st and December 31st, 2018. We excluded those aged <20 years and those admitted to pediatric, intensive care, and psychiatric wards. Finally, 9273 patients were included. We reviewed the incidence in these patients of accidental falls reported to the medical safety department. We noted whether these patients received trazodone, quetiapine, or risperidone. We also observed whether they were taking a benzodiazepine receptor agonist, which is a known risk factor. We further examined each patient's age, sex, the department they were visiting, and their diseases. Patients were considered to have taken medication if it was administered within 24 hours before an accidental fall. Multiple logistic regression analysis was used to evaluate the risk of accidental fall.

Results: Multivariate analysis showed that the adjusted odds ratios (OR) for each medication (with 95% confidence intervals) were: trazodone (OR, 0.47 [0.27–0.80]), quetiapine (OR, 1.06 [0.46–2.46]), and risperidone (OR, 0.82 [0.41–1.63]).

Conclusion: The association of risperidone and quetiapine with accidental falls was unclear. Interestingly, however, trazodone may help reduce the risk, which makes it a potential pharmacologic treatment option for insomnia in patients at high risk for accidental falls.

KEYWORDS

accidental fall, insomnia, quetiapine, risperidone, trazodone

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1 | INTRODUCTION

Accidental falls are associated with multiple risk factors such as medical history, physical function, environment, and medications.¹ In addition to physical trauma, falls produce fear of falling, which is associated with activity limitation and the loss of independence.² It is important to prevent the first accidental fall. For this prevention, it is necessary to understand the risk factors of individual patients.

Patients who are elderly, cognitively impaired, or severely ill are at risk for delirium,³ and they are commonly prescribed antidepressants and antipsychotics for insomnia.^{4,5} Although antidepressants and antipsychotics have been reported as risk agents for falls,⁶ no consensus has been reached on the risk posed by individual agents. For example, risperidone may increase the risk of falls,⁷ whereas others may decrease it.⁸ Therefore, information on the risk of falls for individual drugs is lacking. With the aim of adding information on the risk of falls, this study evaluated the risk of falls with trazodone, risperidone, and quetiapine use, which are recommended at Kanazawa Medical University Hospital as treatment for insomnia in patients at risk of delirium.

2 | MATERIALS AND METHODS

2.1 | Study design

This case-control study was conducted at Kanazawa Medical University Hospital, an 817-beds regional hospital with 39 departments that provide acute care. We used multiple logistic regression analysis to evaluate risk factors for accidental falls. The study was approved by the hospital's Ethical Review Committee (No. H297) and conducted in accordance with the Declaration of Helsinki.

Our report complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.⁹

2.2 | Patients

The number of patients to experience accidental falls was expected to be 10 times greater than the number of explanatory variables. Therefore, we examined a one-year period (January 1st to December 31st, 2018). We included patients who were hospitalized during this period, except for those aged <20 years of age or who were admitted to the pediatric, intensive care, or psychiatric wards, which have different nursing systems than the general wards. At Kanazawa Medical University Hospital, accidental falls must be reported to the medical safety department. Patients who experienced accidental falls were defined as those who reported a fall during the study period (Figure 1). Patients who had fallen more than once during the study period were investigated for their first accidental fall.

2.3 | Data collection

Data were retrospectively extracted from medical records. The use of antidepressants and antipsychotics was confirmed [i.e., trazodone, quetiapine and risperidone, which are recommended for use at the hospital]. The drug use history was included even if it was used for the treatment of conditions other than insomnia, such as restlessness, delirium, and behavioral and psychological symptoms of dementia. The following previously-reported risk factors for accidental falls were ascertained: age ≥ 70 years,^{6,10} male,¹¹ length of hospital stay ≥ 14 days,¹² and use of benzodiazepine receptor agonists.¹¹ Furthermore, the occurrence of the following was recorded:

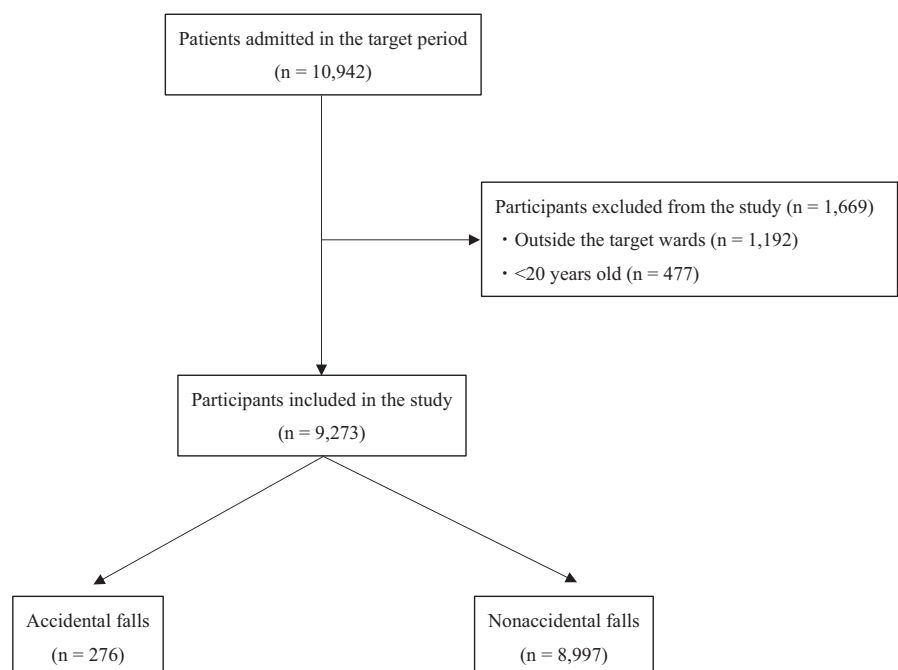


FIGURE 1 Flowchart of patient selection according to the inclusion criteria for the study



dementia,¹³ stroke,¹⁴ depression and diabetes,¹⁵ Parkinson's disease,^{14,16} and whether or not the patient was admitted any of the following departments: neurosurgery,^{14,17} neurology,^{14,16,18} cardiology,^{19,20} ophthalmology,²⁰ and orthopedics.^{15,21} Among benzodiazepine receptor agonists, we noted triazolam because of its reported high risk of falls¹¹; brotizolam and zolpidem were noted because of their high prescription volume at our hospital. Patients who fell were considered to have taken medication if it was administered within 24 hours before the accidental fall. Dementia was defined as Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, and vascular dementia. Stroke was defined as lacunar infarction, atherothrombotic infarction, cardiogenic cerebral embolism, subarachnoid hemorrhage, putaminal hemorrhage, thalamic hemorrhage, brainstem hemorrhage, cerebellar hemorrhage, and subcortical hemorrhage.

2.4 | Statistical analysis

Comparison of categorical data between the two groups was performed using the chi-squared test with Yates' correction. Multivariate analysis was performed by logistic regression analysis, using the presence or absence of accidental falls as the objective variable. Explanatory variables included the presence or absence of trazodone, quetiapine, and risperidone, as well as significant factors ($P < 0.1$) identified in univariate analysis. Analyses were performed using SPSS version 22 (IBM), using a two-sided significance level of 0.05.

3 | RESULTS

3.1 | Patient backgrounds

Of the 10 942 patients who were admitted during the study period, we excluded 1192 who were not admitted to the targeted wards and 477 who were aged < 20 years. Of the remaining 9273 study patients, 276 experienced accidental falls—an incidence rate of 3.0% (Figure 1). The patients' backgrounds are shown in Table 1.

To determine the variables for multivariate analysis, we performed univariate analysis of previously-reported risk factors for accidental falls, as follows: age ≥ 70 years, male, length of hospital stay ≥ 14 days, use of brotizolam, use of triazolam, neurology, neurosurgery, ophthalmology, dementia, diabetes, and stroke (Table 2).

3.2 | Effects of trazodone, quetiapine, and risperidone on accidental falls

Multivariate analysis calculated adjusted odds ratios (OR) with 95% confidence intervals for quetiapine (OR, 1.06 [0.46–2.46]) and risperidone (OR, 0.82 [0.41–1.63]); they were not significant

independent factors associated with accidental falls. However, trazodone (OR, 0.47 [0.27–0.80]) was a significant independent factor associated with reducing the risk of accidental falls (Table 3).

Other items detected as independent risk factors significantly associated with accidental falls were triazolam (OR, 2.31 [1.03–5.20]), age ≥ 70 years (OR, 2.24 [1.69–2.97]), male (OR, 1.39 [1.08–1.80]), length of stay ≥ 14 days (OR, 3.88 [2.95–5.10]), neurosurgery (OR, 3.96 [2.48–6.33]), and dementia (OR, 3.00 [2.06–4.36]). Ophthalmology (OR, 0.31 [0.13–0.77]) was independently, significantly associated with reducing the risk of accidental falls (Table 3).

4 | DISCUSSION

We evaluated the effects of the antidepressant trazodone and the antipsychotics quetiapine and risperidone on accidental falls. For quetiapine and risperidone, the effects on accidental falls were unclear; however, trazodone was found to reduce the risk of accidental falls. A possible reason is that trazodone improves insomnia²² and delirium,²³ which are both risk factors for falls. Trazodone prolongs slow-wave sleep duration and improves sleep quality through 5-HT_{2A} receptor blockade.²⁴ Avidan et al.²⁵ reported that sleep medication reduced the risk of falls due to insomnia. Trazodone improves sleep–wake disturbances, one of the factors of delirium, by blocking 5-HT_{2A} receptors and decreases the severity of delirium within a short period of administration.²⁴ Moreover, Trazodone has a short half-life of 3–6 hours and causes less drowsiness during the day.²⁶ These results support our findings.

On the contrary, trazodone can increase the risk of falls.²⁷ Its side effects of drowsiness and dizziness are thought to contribute to this risk.²⁷ Furthermore, drowsiness can be induced in a dose-dependent manner.²⁶ It is possible that our hospital's recommendation to initiate trazodone at a lower dose may have contributed to our different results, compared with those previously-reported. When trazodone is used for the treatment of insomnia, it is recommended to start with a 25 mg dose, which is the practice at Kanazawa Medical University Hospital. The present study confirmed that the patient had taken the medication within 24 h prior to the fall. In the previous report, only the presence or absence of prescription was confirmed, not whether the patient had taken the medication. This point may have affected the results. This study has several limitations. The risk factors we identified (triazolam use, age ≥ 70 years, male, length of stay ≥ 14 days, neurosurgery, and dementia) were consistent with previous reports.^{6,10–14,17} However, our results differed for ophthalmology. Most patients were admitted to the ophthalmology ward for cataract

TABLE 1 Characteristics of participants included in the study

Age, median (IQR)	68	(56, 77)
Male, n (%)	4981	(54)
Hospitalization period, median (IQR)	7	(2, 17)

Abbreviation: IQR, interquartile range.

TABLE 2 Univariate analysis of patient background factors

	Accidental fall		Non-accidental fall		P-value ^a
	(n = 276)	(%)	(n = 8997)	(%)	
Age ≥ 70 years	196	(71.0)	4038	(44.9)	<0.001
Male	170	(61.6)	4811	(53.5)	0.009
Length of hospital stay ≥14 days	192	(69.6)	2724	(30.3)	<0.001
Medication					
Brotizolam	14	(5.1)	262	(2.9)	0.057
Trazodone	17	(6.2)	474	(5.3)	0.607
Triazolam	7	(2.5)	78	(0.9)	0.011
Quetiapine	7	(2.5)	101	(1.1)	0.061
Risperidone	11	(4.0)	160	(1.8)	0.014
Zolpidem	13	(4.7)	363	(4.0)	0.685
Hospital department					
Cardiology	31	(11.2)	891	(9.9)	0.532
Neurology	15	(5.4)	213	(2.4)	0.002
Neurosurgery	28	(10.1)	212	(2.4)	<0.001
Ophthalmology	5	(1.8)	902	(10.0)	<0.001
Orthopedics	26	(9.4)	771	(8.6)	0.698
Concomitant disease					
Dementia	46	(16.7)	327	(3.6)	<0.001
Depression	7	(2.5)	114	(1.3)	0.119
Diabetes	81	(29.3)	1834	(20.4)	<0.001
Parkinson's disease	3	(1.1)	41	(0.5)	0.290
Stroke	36	(13.0)	330	(3.7)	<0.001

^aChi-square test with Yates correction. Variables are expressed as n (%).

TABLE 3 Multiple logistic regression analysis of the risk of accidental fall

Variables	Adjusted OR	95% CI	P-value
Trazodone	0.47	(0.27, 0.80)	0.006
Quetiapine	1.06	(0.46, 2.46)	0.890
Risperidone	0.82	(0.41, 1.63)	0.570
Brotizolam	1.30	(0.73, 2.30)	0.369
Triazolam	2.31	(1.03, 5.20)	0.042
Age ≥ 70 years	2.24	(1.69, 2.97)	<0.001
Male	1.39	(1.08, 1.80)	0.011
Length of hospital stay ≥14 days	3.88	(2.95, 5.10)	<0.001
Neurology	1.11	(0.60, 2.07)	0.734
Neurosurgery	3.96	(2.48, 6.33)	<0.001
Ophthalmology	0.31	(0.13, 0.77)	0.011
Dementia	3.00	(2.06, 4.36)	<0.001
Diabetes	1.27	(0.96, 1.67)	0.092
Stroke	1.55	(0.99, 2.42)	0.053

Abbreviations: OR: odds ratio; CI: confidence interval.

surgery, performed the day after admission. We speculate that early improvement of visual impairment after admission may have reduced the risk of accidental falls. Because this study was conducted at a

single institution, there is a possibility of bias regarding the content of medical care and the nursing system. However, the 3% rate of accidental falls is comparable to previously-reported rates^{28,29} of 1.3% and 1.6% in acute care university hospitals. This suggests that our hospital is an appropriate facility to evaluate accidental falls.

In our analyses, we adjusted the medications and diseases that are risk factors for accidental falls. However, the nursing system, motor function, sleep status, and other drugs that may be fall risks, such as suvorexant, the number of concomitant medications, and drug dosages, were not thoroughly investigated and the effects of confounding factors may have intervened. In particular, delirium has been a contributor to accidental falls but it could not be accurately investigated in this retrospective study. However, our results are consistent with the established relationship between insomnia, delirium, and falls, considering the effects of trazodone on sleep and improvement of delirium. We could not investigate the history of falls,¹ which is a risk factor for falls, but we minimized this effect by investigating the first fall during the study period. Future studies are needed to investigate the relationship between insomnia, delirium, and falls, possibly by adding further risk factors as explanatory variables or by conducting randomized controlled trials.

Although we did not determine the effects of quetiapine and risperidone, used as insomnia medications, on accidental falls, we found that that trazodone may reduce the risk of falls. Trazodone



may be an option for the treatment of insomnia in patients at high risk of accidental falls.

AUTHOR CONTRIBUTIONS

Yoshihito Shimizu and Masatoshi Taga contributed to the design of the study and drafting of the manuscript. Yoshihito Shimizu and Yasuhiko Yamamoto collected the data. Yoshihito Shimizu and Masatoshi Taga conducted the statistical analysis. Yoshimitsu Takahashi and Togen Masauji participated in the interpretation of data for the study. All authors contributed to the critical revision of the manuscript and approved the final version of the manuscript to be published.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors cannot make the data publicly available because of restrictions imposed by the ethics committee. Furthermore, the opt-out clearly states that the information will not be disclosed.

ETHICAL APPROVAL

The study was approved by the hospital's Ethical Review Committee (No. H297) and conducted in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

The requirement to obtain informed consent was waived in this study because the data were retrospectively extracted from electronic medical charts.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

We did not reproduce material from other sources.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

Not applicable.

ANIMAL STUDIES

n/a

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