ORIGINAL RESEARCH

Zolpidem Is Independently Associated With Increased Risk of Inpatient Falls

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BACKGROUND: Inpatient falls are associated with significant morbidity and increased healthcare costs. Zolpidem has been reported to decrease balance and is associated with falls. Yet, it is a commonly used hypnotic agent in the inpatient setting. Zolpidem use in hospitalized patients may be a significant and potentially modifiable risk factor for falling.

OBJECTIVE: To determine whether inpatients administered zolpidem are at greater risk of falling.

DESIGN: Retrospective cohort study.

SETTING: Adult non-intensive care unit (non-ICU) inpatients at a tertiary care center.

METHODS: Adult inpatients who were prescribed zolpidem were identified. Electronic medical records were reviewed to capture demographics and other risk factors for falls. The fall rate was compared in those administered zolpidem versus those only prescribed zolpidem. Multivariate analyses were performed to determine whether zolpidem was independently associated with falls.

RESULTS: The fall rate among patients who were prescribed and received zolpidem (n = 4962) was significantly greater than among patients who were prescribed but did not receive zolpidem (n = 11,358) (3.04% vs 0.71%; $P < 0.001$). Zolpidem use continued to remain significantly associated with increased fall risk after accounting for age, gender, insomnia, delirium status, dose of zolpidem, Charlson comorbidity index, Hendrich's fall risk score, length of hospital stay, presence of visual impairment, gait abnormalities, and dementia/cognitive impairment (adjusted odds ratio [OR] 4.37, 95% confidence interval [CI] = 3.34–5.76; $P < 0.001$). Additionally, patients taking zolpidem who experienced a fall did not differ from other hospitalized adult patients who fell in terms of age, opioids, antidepressants, sedative-antidepressants, antipsychotics, benzodiazepine, or antihistamine use.

CONCLUSION: Zolpidem use was a strong, independent, and potentially modifiable risk factor for inpatient falls. *Journal of Hospital Medicine* 2013;8:1–6. © 2012 Society of Hospital Medicine

Hospitalized patients have increased rates of sleep disturbances.[1,2] Sleep disturbances are perceived to be disruptive to both patients and staff, a putative reason for the high rates of hypnotic use in hospitalized patients.[3,4] Zolpidem, a short-acting, non-benzodiazepine, benzodiazepine receptor agonist that acts at the γ-aminobutyric acid (GABA)-A receptor complex, is the most commonly prescribed hypnotic agent in the United States.[5,6] It is also extremely commonly used in inpatient settings. Although zolpidem is thought to have a relatively benign side-effect profile, it has been found to impair balance in healthy volunteers, even after a single dose.[7] Zolpidem use has been found to be higher in community-dwelling adults who sustained a hip fracture.[8,9]

Falls in the inpatient setting are associated with significantly increased morbidity, serious injury, and can result in a prolonged hospital stay and increased healthcare expenditure.[10,11] It is for these reasons that fall reduction is one of the target aims of the Department of Health and Human Services Partnership for Patients.[10] While many fall prevention programs have been shown to be effective, they are resource intensive.[11] If zolpidem use were associated with increased rates of falls in hospitalized patients, decreasing zolpidem prescription could be an easy and effective intervention in order to reduce fall risk.

A previous case-control study showed increased zolpidem use in geriatric inpatients who sustained a fall.[8] However, the literature linking zolpidem use with an increased fall risk in hospitalized patients is based upon a small sample and does not correct for potential confounders, such as other medication use, delirium, or insomnia.[8]

We aimed to conduct a cohort study in a large inpatient teaching hospital to ascertain whether zolpidem is associated with increased rates of falls after accounting for age, sex, insomnia, delirium, and use of other medications previously shown to be associated with increased fall risk.

METHODS

All inpatients 18 years or older, admitted in 2010 to hospitals at Mayo Clinic, Rochester, MN, who were prescribed zolpidem were eligible for inclusion in the study. We excluded all patients who were pregnant and those in the intensive care unit (ICU) setting. We compared the group that was prescribed zolpidem and received it, to the group that was prescribed zolpidem but did not receive the medication. We restricted the analysis to patients who were prescribed zolpidem because there may be systematic differences between patients eligible to receive zolpidem and patients in whom zolpidem is not prescribed at all. Our institutional admission order sets provide physicians and other healthcare providers an option of selecting as-needed zolpidem or trazodone as sleep aids. Zolpidem was the most common sleep aid that was prescribed to inpatients with a ratio of zolpidem to trazodone prescriptions being 2:1.

We used the pharmacy database to identify all eligible inpatients who were prescribed or administered either scheduled or "as needed" (PRN) zolpidem during the study period. All details regarding zolpidem prescription and administration were obtained from the inpatient pharmacy electronic database. This database includes all zolpidem orders that were placed in the inpatient setting. The database also includes details of dose and time of all zolpidem administrations.

The institution uses electronic medication profiles, and automated dispensing machines with patient profiles and point-of-care barcode scan technology, which forces highly accurate electronic documentation of the medication administered. The documentation of medication not given or patient refusal would be documented as not administered.

We reviewed the electronic medical record to ascertain demographics, as well as diagnoses of visual impairment, gait abnormality, cognitive impairment/dementia, insomnia, and delirium, based on International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for these conditions (see Supporting Information, Appendix 1, in the online version of this article). These diagnostic codes were electronically abstracted from the medical record. The diagnosis codes are entered by medical coding specialists based on review of all provider notes. Hospital length of stay, Charlson comorbidity index scores, and Hendrich's fall risk scores from day of admission were abstracted from the individual electronic medical records. The nursing staff at our institution perform all the requisite assessments and electronically input all components required to calculate a Hendrich's fall risk score upon admission.

The Charlson index is a composite score calculated based on a patient's medical comorbidities. Each comorbidity is designated a score of 1, 2, 3, or 6 based on the risk of mortality associated with that condition.[12] The Hendrich's fall risk is calculated based on the patient's current medication regimen, level of alertness, current medical condition, and the "get up and go" test.[13] A score of 5 or greater indicates increased risk of falling. These scores from the day of admission were available for all patients and were extracted from the nursing flow sheet.

At our institution, all falls are required to be called into a central event reporting system, and each fall receives an analysis regarding risk factors and proximal causes. We obtained details of all inpatient falls from this event system. The medication administration record, a part of the patient's electronic medical record, was accessed to identify all medications administered in the 24 hours prior to the fall. Medications were grouped into their respective pharmacologic classes. Antidepressants, antipsychotics, antihistamines, sedative antidepressants (this class included trazodone and mirtazapine), benzodiazepines, and opioids were included in the analyses. These medications have previously been shown to be associated with increased risk of falls.[14]

Statistical analyses were performed using JMP (version 9.03, Cary, NC). Univariate analyses were performed to calculate the odds ratio of falling in inpatients who were administered zolpidem, in male patients, those admitted to a surgical floor, and in those that had a diagnosis of insomnia, visual impairment, gait abnormality, cognitive impairment/dementia, or delirium. Hospital length of stay, age, zolpidem dose, Charlson comorbidity index scores, and Hendrich's fall risk scores were treated as continuous variables, and odds ratio of falling per unit increase was calculated for each of these variables.

Multivariable logistic regression analysis was performed to calculate the odds of falling in patients who received zolpidem, after accounting for age, gender, insomnia, visual impairment, gait abnormality, cognitive impairment/dementia, delirium, hospital length of stay, zolpidem dose, Charlson comorbidity index scores, and Hendrich's fall risk scores. Logistic regression analyses was repeated with only those factors that were significantly associated ($P < 0.05$) with falls or factors where the association was close to statistical significance ($P < 0.08$).

To account for the presence of other medications that might have increased fall risk, separate analyses using the Mann–Whitney U test comparing medication use in all hospitalized patients who sustained a fall were performed. We compared the rates of use of antidepressants, antipsychotics, antihistamines, sedative antidepressants (this class included trazodone and mirtazapine), benzodiazepines, and opioid medication in patients who were administered zolpidem to those patients not administered zolpidem in the 24 hours prior to sustaining a fall. This study had the requisite institutional review board approval.
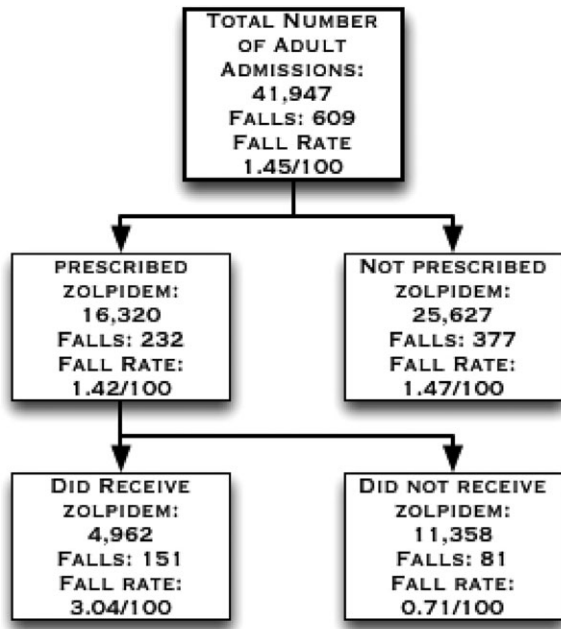
FIG. 1. Breakdown of patient population and fall risk as it relates to zolpidem order and administration.

TABLE 1. Demographic Characteristics of All Patients Who Were Prescribed Zolpidem

Characteristics	Zolpidem Administered N = 4962 (%)	Zolpidem Not Administered N = 11,358 (%)	P Value
Age	56.84 ± 17.24 y	53.8 ± 18.30 y	<0.0001
Males	2442 (49.21)	4490 (39.53)	<0.0001
Falls	151 (3.04)	81 (0.71)	<0.0001
Insomnia	1595 (32.3)	1942 (17.1)	<0.0001
Delirium	411 (8.28)	378 (3.33)	<0.0001
Cognitive impairment	38 (0.77)	63 (0.55)	0.11
Visual impairment	84 (1.69)	198 (1.74)	0.82
Gait abnormalities	814 (16.40)	1761 (15.50)	0.15
Patients on surgical floors	2423 (48.8)	5736 (50.50)	0.05
Length of hospital stay (mean/SD)	4.26 ± 8.03 d	4.18 ± 8.07 d	0.60
Charlson index (mean/SD)	4.07 ± 3.81	3.76 ± 3.70	<0.0001
Hendrich's fall risk score (mean/SD)	1.97 ± 1.93	1.91 ± 1.97	0.08

Abbreviations: SD, standard deviation.

RESULTS

There were 41,947 eligible admissions during the study period. Of these, a total of 16,320 (38.9%; mean age 54.7 ± 18 years) patients were prescribed zolpidem. Among these patients, 4962 (30.4% of those prescribed, or 11.8% of all admissions) were administered zolpidem during the study period (Figure 1). The majority (88%) of zolpidem prescriptions were for PRN or "as needed" use. Patients who received zolpidem were older than those who were prescribed the medication but did not receive it (56.84 ± 17.2 years vs 53.79 ± 18.31 years; $P < 0.001$).

Patients who were prescribed and received zolpidem were more likely to be male, or have insomnia or delirium. They had higher Charlson comorbidity index scores and were more likely to be on a surgical floor. There was no statistically significant difference between patients who received zolpidem and patients who were prescribed but did not receive zolpidem in terms of their fall risk scores, length of hospital stay, rates of visual impairment, gait abnormalities, and cognitive impairment/dementia (all $P > 0.05$) (Table 1).

During the study period, there were a total of 672 total falls, with 609 unique patients falls (fall rate of 1.45/100 patients). Those who were administered zolpidem had an increased risk of falling compared to patients who were prescribed, but were not administered, zolpidem (fall rate of 3.04/100 patients vs 0.71/100 patients; odds ratio [OR] = 4.37, 95% confidence interval [CI] = 3.33–5.74; $P < 0.001$). Additionally, patients who received zolpidem had an increased risk of falling, as opposed to all other adult inpatients who did not receive zolpidem—whether prescribed zolpidem or not (3.04 falls/100 patients vs 1.24 falls/100 patients; OR = 2.50, 95% CI = 2.08–3.02; $P < 0.001$). The absolute increase in risk of sustaining a fall after receiving zolpidem as compared to all other adult inpatients was 1.8%, revealing a number needed to harm of 55.

During the study period, a total of 21,354 doses of zolpidem were administered, revealing a fall rate of 0.007 falls per dose of zolpidem administered (151/21,354). This was significantly greater than the baseline fall risk of 0.0028 falls per day of hospitalization (672/240,015 total hospital days) ($P < 0.0001$).

On univariate analyses, zolpidem use (OR = 4.37; 95% CI = 3.34–5.76; $P < 0.001$), male sex (OR = 1.36; 95% CI = 1.05–1.76; $P = 0.02$), insomnia (OR = 2.37; 95% CI = 1.81–3.08; $P < 0.01$), and delirium (OR = 4.96; 95% CI = 3.52–6.86; $P < 0.001$) were significantly associated with increased falls, as were increasing age, Charlson comorbidity index scores, fall risk scores, and dose of zolpidem (Table 2). While the association between the presence of cognitive impairment/dementia and falling was close to significant (OR = 2.89; 95% CI = 0.88–6.98; $P = 0.075$), the association between fall risk and the presence of visual impairment, gait abnormalities, and being on a surgical floor was not statistically significant.

Zolpidem use continued to be significantly associated with increased fall risk (adjusted OR = 6.39; 95% CI = 3.07–14.49; $P < 0.001$) after multivariable logistic regression analyses accounting for all factors where the association with increased fall risk was statistically significant or close to significant on univariate analyses (Table 3). On further analyses, of all adult non-ICU, non-pregnant inpatients who sustained a fall, those who sustained a fall after receiving zolpidem did not differ from other inpatients who did not sustain a fall in terms of their age (59.6 ± 17.95 vs 63.2 ± 16.8 years; $P = 0.07$), antidepressant (42.62%

TABLE 2. Univariate Analysis of Potential Risk Factors for Falling in All Patients Prescribed Zolpidem

Risk Factor	Odds Ratio of Falling	Lower Confidence Interval*	Upper Confidence Interval*	*P* Value
Zolpidem administration	4.37	3.34	5.76	<0.001
Male sex	1.36	1.05	1.76	0.02
Insomnia	2.37	1.81	3.08	<0.001
Delirium	4.96	3.52	6.86	<0.001
Cognitive impairment	2.89	0.88	6.98	0.075
Visual impairment	1.26	0.44	2.76	0.63
Gait abnormalities	1.22	0.86	1.68	0.26
Being on a surgical floors	0.88	0.68	1.15	0.36
Age[†]	1.01	1.01	1.02	<0.001
Length of hospital stay[‡]	0.99	0.98	1.01	0.93
Charlson index[§]	1.29	1.26	1.32	<0.001
Hendrich's fall risk score[‖]	1.36	1.29	1.42	<0.001
Dose of zolpidem[¶]	1.21	1.17	1.26	<0.001

* 95% Confidence intervals;
[†] per 1 year increase in age;
[‡] per 1 day increase in length of hospital stay;
[§] per unit increase in Charlson score;
[‖] per unit increase in Hendrich's fall risk score;
[¶] per 1 mg increase in dose.

TABLE 3. Multivariate Analysis of Potential Risk Factors for Falls

Characteristic	Adjusted Odds Ratio of Falling	Lower Confidence Interval*	Upper Confidence Interval*	*P* Value
Zolpidem administration	6.39	3.07	14.49	<0.001
Male sex	1.24	0.93	1.67	0.14
Insomnia	1.60	1.17	2.17	0.003
Delirium	2.62	1.73	3.88	<0.001
Cognitive impairment	1.47	0.33	4.53	0.56
Age[†]	1.04	1.03	1.05	<0.001
Hendrich's fall risk score[‡]	1.30	1.23	1.36	<0.001
Charlson index[§]	1.33	1.29	1.36	<0.001
Dose[‖]	0.94	0.82	1.06	0.37

* 95% Confidence intervals;
[†] per 1 year increase in age;
[‡] per unit increase in Hendrich's fall risk score;
[§] per unit increase in Charlson index;
[‖] per 1 mg increase in dose.

vs 39.70%; *P* = 0.39), antipsychotic (9.83% vs 13.78%; *P* = 0.24), antihistamine (6.55% vs 3.49%; *P* = 0.10), sedative antidepressant (14.75% vs 15.80%; *P* = 0.31), benzodiazepine (36.06% vs 26.86%; *P* = 0.83), or opioid use (55.73% vs 43.01%; *P* = 0.66).

DISCUSSION

In this study, zolpidem use was associated with an increased risk of falling in hospitalized patients. We calculate that for every 55 inpatients administered zolpidem, we might expect one more fall than would otherwise have occurred. To our knowledge, this is the largest study examining the association between zolpidem use and falls in an inpatient setting. Previous literature have not accounted for the presence of several other factors that could increase fall risk in hospitalized patients using zolpidem, such as visual impairment, gait abnormalities, and type of admission. In our study, insomnia and delirium were associated with higher rates of falls, however, the risk of sustaining a fall after receiving zolpidem continued to remain elevated even after accounting for these and multiple other risk factors.

Previous research in healthy volunteers found that subjects who received zolpidem experienced increased difficulty maintaining their balance.[15,16] The subject's ability to correct their balance, with their eyes closed and also with their eyes open, was adversely affected, indicating that both proprioception and visually enabled balance correction were impacted. Navigating obstacles in a hospital setting, where the patient is in a novel environment and on other medications that could impact balance, is potentially made significantly worse by zolpidem, thus resulting in an increased fall risk.

While a previous case-control study of inpatients, 65 years and older, reported increased rates of zolpidem use among inpatients who sustained a fall, it did not report whether this association continued to remain significant after accounting for potential confounders.[9] Another study, in a similar age group and carried out in an ambulatory community setting, found that patients who sustained a hip fracture were more likely to have received zolpidem in the 6 months prior to their fall.[8] In this study, zolpidem use continued to be significantly associated with hip fractures after accounting for potential confounders such as the use of other medication, age, comorbidity index score, the number of hospital days, and the number of nursing days. Our study differs from these studies in that it was a cohort study in an inpatient setting, and we included all non-pregnant adult hospitalized patients outside of the ICU. Also, we examined medication administration in the 24 hours prior to a fall rather than medications simply prescribed in the months prior to a fall.[8] In our cohort of adult inpatients, the odds of zolpidem use among patients who fell was greater than those previously reported. This could indicate increased vulnerability in hospitalized patients compared to community-dwelling elderly.

Insomnia, older age, and delirium have all been shown to be associated with an increased risk of falls in previous research.[15–17] In one study of community-dwelling older adults, the authors found a higher risk of falling in subjects with insomnia, but not in those who received a hypnotic agent.[15] Delirium increases the likelihood of nocturnal wandering, also associated with increased risk of fall. Our inpatient cohort study confirms these prior findings: insomnia, delirium, and older age were all associated with an increased risk of falling. However, zolpidem use continued to remain a significant risk factor for falls even after accounting for these risk factors.

Hospitalized patients are more likely to be physically compromised and on a greater number of medications compared to community-dwelling subjects, and hence at increased risk of falling. Multiple classes of medications have been shown to be associated with an increased fall risk in hospitalized patients.[14] In our study, the patients who sustained a fall after receiving zolpidem did not differ from other patients who sustained a fall in terms of their medication use. Zolpidem thus appears to increase the risk of falling beyond that attributable to other medications in hospitalized patients.

A recent United States Preventive Services Task Force on Prevention of Falls in Community Dwelling Older Adults recommendation indicates that withdrawal of medication alone does not appear to have a significant impact on fall rates.[18] Another study indicates that reduced benozodiazepine use did not significantly reduce the rates of hip fractures in the community.[19] While these studies indicate that fall risk is multifactorial and requires a complex set of interventions, our results indicate that there might be an association between zolpidem administration and falls in an inpatient setting. Changing order sets so that zolpidem use is not encouraged could potentially reduce fall rates in hospitalized patients, a step that we have already taken in our institution based upon these findings. Other potential measures to reduce fall risk include the use of fall precautions in patients who are prescribed zolpidem or use of non-pharmacologic treatments for insomnia. However, these interventions would need to be empirically tested before they could be recommended with confidence.

The results of this study must be viewed in the light of some limitations. Although we included age, sex, zolpidem dose, length of hospital stay, Charlson comorbidity index score, fall risk score, and diagnoses of insomnia, visual impairment, gait abnormality, cognitive impairment/dementia, and delirium in our analyses, we were unable to account for the degree of severity of these conditions. There could also be other possible medical conditions that result in an increased risk of falling that were not accounted for in our analyses. While we did attempt to correct for insomnia and delirium diagnoses, transient complaints of insomnia or altered mental status may have been missed by our retrospective methodology, and perhaps could co-associate with risk of falling. Furthermore, administration of zolpidem was associated with a higher risk of falls when compared to other patients who were prescribed zolpidem, and also when compared to all other patients regardless of zolpidem prescription. We used ICD-9 codes to identify patients with insomnia, delirium, visual impairment, and gait abnormalities, and these could be prone to misclassification and possible ascertainment bias. Finally, we were unable to account for use of medications that might potentially increase the risk of falling in the entire cohort. We were, however, able to account for this in the subset of patients who sustained a fall, and did not note a difference between the group that received zolpidem and the group that did not. In these analyses, we were able to account for administration of these other medications, but not the dose or cumulative dose.

CONCLUSIONS

Our study, the largest in an inpatient cohort, reveals that zolpidem administration is associated with increased risk of falling even after accounting for insomnia, delirium, and multiple other risk factors. Patients who sustained a fall after receiving zolpidem did not differ from other patients who sustained a fall, in terms of age or use of other medications conferring increased fall risk. Although insomnia and delirium are also associated with an increased risk of falling, addition of zolpidem in this situation appears to result in a further increase in fall risk. Presently, because there is limited evidence to recommend other hypnotic agents as safer alternatives in inpatient settings, non-pharmacological measures to improve the sleep of hospitalized patients should be investigated as preferred methods to provide safe relief from complaints of disturbed sleep.

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