Relationship Between Zolpidem Use and Stroke Risk: A Taiwanese Population–Based Case-Control Study

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ABSTRACT

Objective: To evaluate the relationship between the use of zolpidem and risk of subsequent stroke in Taiwanese patients.

Method: This case-control study used data obtained from the National Health Insurance Research Database to determine whether the use of zolpidem is associated with an increased risk of stroke. The case group comprised 12,747 patients who were newly diagnosed with stroke between January 1, 2005, and December 31, 2009. We also randomly selected a 4-fold greater number of patients without stroke as a control group. Patients with ischemic and hemorrhagic stroke were frequency-matched with controls on sex, age, and year of index date. We measured the effect of zolpidem and determined the adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Results: We found that exposure to zolpidem was associated with increased risk of ischemic stroke (OR = 1.37; 95% CI, 1.30–1.44). The risk of ischemic stroke increased significantly with increasing exposure to zolpidem; for average exposures of ≤ 70, 71–470, and > 470 mg per year, the ORs were 1.20, 1.41, and 1.50, respectively; the *P* value for the trend was < .0001. Regardless of whether people presented with a sleep disorder, the risk of stroke was still greatly increased with zolpidem exposure; the adjusted OR was 1.37 without sleep disorder and 1.41 with sleep disorder.

Conclusions: This population-based study positively associated the use of zolpidem with increased risk of ischemic stroke. Our findings warrant further large-scale and in-depth investigations in this area.

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Insomnia is common in the general population; it is a distressing condition that limits the ability to sleep adequately at night and affects a person's ability to function effectively during waking hours.[1] Research studies often define insomnia as sleep latency (time taken to fall asleep) greater than 30 minutes, sleep efficiency (time asleep:time in bed) of less than 85%, or sleep disturbance more often than 3 times per week.[2] Various studies have reported that approximately 30% of adults report 1 or more insomnia symptoms.[3] Symptoms include difficulty initiating sleep and/or maintaining sleep, waking up too early, daytime somnolence, and nonrestorative or poor-quality sleep.[4] The consequences of the condition can vary from mild sleepiness to more severe psychiatric disturbances and ischemic stroke.[5,6]

Stroke is the second leading cause of death globally[7] and is the leading cause of disability in adults.[8] Identification of risk factors for stroke is important for the prevention of stroke recurrence.

Zolpidem is a nonbenzodiazepine hypnotic agent that belongs to a class of psychotropic drugs that enhance γ-aminobutyric acid type A ($GABA_A$) receptor function.[9,10] A single-blind trial[11] published in 1991 investigated the nightly use of zolpidem for up to 6 months; the authors concluded that 10 mg/d is an appropriate starting dose and is effective and safe for the treatment of various sleep disorders. However, information on possible relationships between the use of zolpidem and the risk of stroke is scant. Researchers recognize that a drug's effectiveness, adverse effects, and interactions are difficult to assess prior to the approval of a medication and may become evident only after the drug has been used by millions of people over an extended period. Zolpidem was the most commonly prescribed agent for insomnia in 2001[12] and remains the Taiwan market leader to the present day. Therefore, even a minor hazard could have important clinical implications and would be of interest to the medical profession and the public.

A large population-based study may help clarify the negative effects of this drug. Thus, we evaluated the relationship between the use of zolpidem and risk of stroke in Taiwanese patients.

METHOD

Data Sources

The National Health Insurance Research Database (NHIRD) stores Taiwan National Health Insurance (NHI) program reimbursement claims data. The program was formed from 13 insurance programs in 1996 and has included approximately 99% of the Taiwan population since 1998. The database is maintained by the National Health Research Institute (NHRI); all personal information is anonymized before release to the public, in the interest of patient privacy.

Our study used a data set containing claims data for 1 million patients randomly selected from the NHIRD Longitudinal Health Insurance Database, for the period 1996–2000. Disease diagnoses, based on outpatient and inpatient files, were made according to the *International Classification of Diseases*, Ninth Revision, Clinical Modification (*ICD-9-CM*).

Clinical Points

- Zolpidem should not be overused, because it is significantly associated with the increased risk of ischemic stroke.
- Zolpidem should be prescribed for the short-term treatment of insomnia or difficulty in getting to sleep.

Study Population

This was a population-based case-control study covering the period from January 1, 2005, to December 31, 2009. Figure 1 shows a flowchart for the selection of the study population. The study identified 10,444 newly diagnosed ischemic stroke patients (*ICD-9-CM* 433–438) and 2,303 hemorrhagic stroke patients (*ICD-9-CM* 430–432) from inpatient files. Patients with a stroke history prior to 2005, aged < 20 years, or with a date of first zolpidem exposure on or later than the date of stroke diagnosis were excluded. The date of newly diagnosed stroke was used as the index date. Patients with ischemic and hemorrhagic stroke were frequency-matched with their controls on sex, age, and year of index date.

Zolpidem exposure was the major risk factor investigated in this study. We collected patients' zolpidem medication histories from before their index dates. We calculated zolpidem average exposure as total zolpidem exposure (mg) ÷ number of years between first exposure and index date.

Stroke comorbidities were considered as covariates. We recorded disease history from before the index date, including hypertension (*ICD-9-CM* 401–405), diabetes (*ICD-9-CM* 250), coronary artery disease (*ICD-9-CM* 410–414), and hyperlipidemia (*ICD-9-CM* 272).

Statistical Analysis

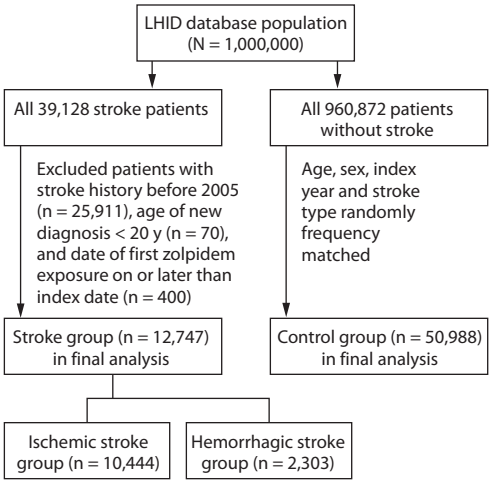
Differences in demographic factors between the 2 study populations were compared using the *t* test for continuous variables and the χ^2 test for categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined by logistic regression and used to evaluate the association between zolpidem exposure and risk of stroke and interactions between zolpidem exposure and stroke comorbidities. We also estimated the association between increasing zolpidem exposure and stroke risk and tested trends in zolpidem exposure by logistic regression.

All data management and analyses were performed using SAS 9.1.3 software (SAS Institute, Cary, North Carolina). All statistical tests were 2-sided, and significance levels were set to .05.

RESULTS

The stroke group and control group had similar mean ages (68 years) and sex ratios (Table 1, $P > .05$). The proposed comorbidities were significantly more frequent in the stroke group than they were in the control group, and the stroke group showed significantly more zolpidem usage than the control group (32.5% vs 22.8%).

Figure 1. Flowchart for Selection of Study Cohort



Abbreviation: LHID = Longitudinal Health Insurance Database.

Table 2 shows associations between zolpidem exposure and risk of stroke. After we adjusted for potential confounding factors, patients with zolpidem exposure had a 1.32-fold greater risk of stroke (95% CI, 1.26–1.38) than people without zolpidem exposure. Risk of stroke increased significantly with increasing levels of zolpidem usage (ORs of 1.15, 1.37, and 1.44 for dosages of ≤ 70, 71–470, and > 470 mg per year, respectively; *P* value for trend < .0001). The zolpidem exposure group had a significantly greater risk of ischemic stroke (OR = 1.37; 95% CI, 1.30–1.44) than the controls, although they did not show a significant risk of hemorrhagic stroke (OR = 1.10; 95% CI, 0.98–1.24). The risk of stroke increased greatly with zolpidem exposure, regardless of whether people had a sleep disorder (OR = 1.41; 95% CI, 1.31–1.53) or did not have a sleep disorder (OR = 1.37; 95% CI, 1.28–1.47) (all *P* values for trend < .0001).

Zolpidem-exposed people who also presented with coronary artery disease, diabetes, hypertension, or hyperlipidemia had a greater risk of stroke (ORs of 2.45, 3.00, 6.14, and 2.23, respectively) than people with zolpidem exposure alone or with a single comorbidity but no exposure (Table 3). These results suggest that zolpidem exposure and stroke comorbidity factors interact to increase the risk of stroke (all *P* values for interaction < .001).

DISCUSSION

This population-based retrospective cohort study demonstrates a significant association between the use of zolpidem and increased risk of ischemic stroke.

Zolpidem dosage also significantly affects stroke risk. Increased zolpidem use is associated with increased risk of ischemic stroke (see Table 2). After adjusting for potential confounding factors, people with zolpidem exposure had a 1.32-fold greater stroke risk (95% CI, 1.26–1.38) than people without zolpidem exposure. Increasing average annual

Table 1. Comparison of Demographic Status and Comorbidities Between Control and Stroke Groups[a]

Variable	Control Group (n = 50,988)	Stroke Group (n = 12,747)	*P* Value
Age, mean (SD), y	67.8 (14.2)	68.0 (14.2)	.1421
Age			
20–39 y	1,892 (3.7)	473 (3.7)	1.0000
40–49 y	3,948 (7.7)	987 (7.7)	
50–59 y	8,520 (16.7)	2,130 (16.7)	
60–69 y	10,960 (21.5)	2,740 (21.5)	
≥ 70 y	25,668 (50.3)	6,417 (50.3)	
Sex			1.0000
Female	21,544 (42.3)	5,386 (42.3)	
Male	29,444 (57.7)	7,361 (57.7)	
Zolpidem exposure			< .0001
No	39,345 (77.2)	8,600 (67.5)	
Yes	11,643 (22.8)	4,147 (32.5)	
Zolpidem average exposure, mg/year			< .0001
None	39,345 (77.2)	8,600 (67.5)	
≤ 70	4,160 (8.2)	1,223 (9.6)	
71–470	3,853 (7.6)	1,430 (11.2)	
> 470	3,630 (7.1)	1,494 (11.7)	
Comorbidity			
Sleep disorder	12,950 (25.4)	3,855 (30.2)	< .0001
Coronary artery disease	14,551 (28.5)	5,166 (40.5)	< .0001
Diabetes	9,182 (18.0)	4,117 (32.3)	< .0001
Hypertension	26,449 (51.9)	10,124 (79.4)	< .0001
Hyperlipidemia	14,599 (28.6)	4,989 (39.1)	< .0001

[a]Data expressed as n (%) unless otherwise noted.

zolpidem exposures of ≤ 70, 71–470, and > 470 mg per year resulted in increases in OR for stroke to 1.15, 1.37, and 1.44, respectively ($P < .0001$ for trend). People with zolpidem exposure were at a significantly greater risk of ischemic stroke (OR = 1.37; 95% CI, 1.30–1.44) than people not exposed to the drug; however, we did not observe a significant association between drug exposure and hemorrhagic stroke (OR = 1.10; 95% CI, 0.98–1.24).

In 2004, a transient improvement in aphasia was observed following ingestion of a first dose of zolpidem by a patient with chronic ischemic stroke.[13] The authors speculated that a lesion, possibly in the lentiform nucleus,[14] impeded the operation of intact structures involved in language production, including Broca's area and the mesial frontal cortex. Zolpidem was assumed to transiently counteract a dynamic diaschisis, allowing for improved function of the residual language network.

In 2010, magnetic resonance imaging and magnetic resonance spectroscopy showed that a stroke patient with complete loss of neuronal viability in the left temporal-parietal region had developed a lesion; single-photon emission computed tomography (SPECT) indicated improved perfusion in the affected hemisphere following administration of low doses of zolpidem.[15] The authors also reported cognitive improvements in Wechsler Adult Intelligence Scale-III and auditory-verbal tasks following treatment with zolpidem. The $GABA_A$ α-1 subunit–mediated desynchronization of elevated low-frequency oscillations alleviated specific dysfunction after low-dosage administration of zolpidem. In a prospective study, Nyakale et al[16,17] correlated brain SPECT changes with Barthel Index scores in 12 stroke patients receiving zolpidem treatment. There were significant improvements in brain perfusion and patient clinical condition in response to zolpidem treatment.

In contrast to these reports in which stroke patients responded positively to zolpidem treatment, the present study shows a significant association between the use of zolpidem and increased risk of ischemic stroke. A possible conclusion is that the consequences of zolpidem exposure far outweigh the effects of sleep disorder.

A cohort of almost 8,000 people was included in a National Health and Nutrition Examination Survey I follow-up study[5] in the United States; an increased adjusted incidence of stroke was found in those who had reported daytime somnolence (OR = 1.4; 95% CI = 1.1–1.8). In a Caerphilly cohort–based study[6] that correlated sleep disorder symptoms to risk of ischemic stroke, risk was increased by roughly 50% in men who reported any single symptom. The risk of stroke was greater in men who reported more than 1 symptom, increasing to a greater than 3-fold risk for men who reported all of the symptoms (OR = 3.63; 95% CI, 1.34–9.84).

Many mechanisms have been proposed to explain the increased vascular risk associated with sleep disturbance; there are reports of increased blood pressure,[18,19] increased carotid atherosclerosis,[20] increased platelet activity,[21,22] changes in the fibrinogen and fibrinolytic systems,[22,23] and changes in other hemostatic factors.[24] Up-regulated C-reactive protein expression has also been reported, suggestive of an inflammatory process.[25] In our study, we noted the same trend for increasing zolpidem exposure in the group of stroke patients without sleep disorder (OR = 1.37) as in the group of stroke patients with sleep disorder (OR = 1.41) (Table 2). Therefore, the significant associations between

Table 2. Odds Ratios for Stroke Occurrence in Individuals With Zolpidem Exposure Relative to Those Without Zolpidem Exposure

Variable	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Overall stroke (n = 63,735)		
Zolpidem exposure		
No	ref	ref
Yes	1.63 (1.56–1.70)	1.32 (1.26–1.38)
Zolpidem average exposure, mg/year		
None	ref	ref
≤ 70	1.35 (1.26–1.44)	1.15 (1.07–1.24)
71–470	1.70 (1.59–1.81)	1.37 (1.28–1.47)
> 470	1.88 (1.77–2.01)	1.44 (1.35–1.54)
P value for trend	< .0001	< .0001
Ischemic stroke (n = 52,220)		
Zolpidem exposure		
No	ref	ref
Yes	1.71 (1.64–1.80)	1.37 (1.30–1.44)
Zolpidem average exposure, mg/year		
None	ref	ref
≤ 70	1.41 (1.31–1.52)	1.20 (1.11–1.30)
71–470	1.78 (1.66–1.91)	1.41 (1.31–1.52)
> 470	2.00 (1.86–2.14)	1.50 (1.40–1.62)
P value for trend	< .0001	< .0001
Hemorrhagic stroke (n = 11,515)		
Zolpidem exposure		
No	ref	ref
Yes	1.25 (1.12–1.40)	1.10 (0.98–1.24)
Zolpidem average exposure, mg/year		
None	ref	ref
≤ 70	1.06 (0.89–1.27)	0.96 (0.79–1.15)
71–470	1.35 (1.14–1.60)	1.21 (1.01–1.44)
> 470	1.37 (1.15–1.63)	1.16 (0.97–1.40)
P value for trend	< .0001	.0247
Without sleep disorder (n = 46,930)		
Zolpidem exposure		
No	ref	ref
Yes	1.69 (1.59–1.8)	1.37 (1.28–1.47)
Zolpidem average exposure, mg/year		
None	ref	ref
≤ 70	1.39 (1.27–1.53)	1.18 (1.07–1.30)
71–470	1.66 (1.49–1.85)	1.31 (1.17–1.47)
> 470	2.55 (2.26–2.88)	1.96 (1.73–2.22)
P value for trend	< .0001	< .0001
With sleep disorder (n = 16,805)		
Zolpidem exposure		
No	ref	ref
Yes	1.54 (1.43–1.66)	1.41 (1.31–1.53)
Zolpidem average exposure, mg/year		
None	ref	ref
≤ 70	1.26 (1.13–1.40)	1.21 (1.08–1.35)
71–470	1.66 (1.51–1.83)	1.53 (1.39–1.69)
> 470	1.64 (1.49–1.80)	1.45 (1.32–1.60)
P value for trend	< .0001	< .0001

[a]Model adjusted for age, gender, coronary artery disease, diabetes, hypertension, and hyperlipidemia.
Abbreviation: ref = reference group.

zolpidem usage and increased risk of ischemic stroke may directly result from the effects of zolpidem itself.

Finally, one of the strengths of this study is the population-based design, with its inherent representativeness. However, the study has some limitations. First, detailed information such as smoking habits, alcohol consumption, body mass index, socioeconomic status, and family history were not available from the NHIRD; all of these variables are possible risk factors for stroke and could plausibly be associated with zolpidem. However, because NHIRD covers almost the entire population of Taiwan and the reimbursement policy is universally the same, it is unlikely that the factors would affect the prescription of zolpidem. Second, the evidence derived from a case-control study is generally of lower quality than that derived from randomized controlled trials because a case-control study design is subject to many biases related to confounding adjustment. Despite our meticulous study design with adequate control of confounding factors, a key limitation is that bias could still remain if there are unmeasured or unknown confounders. Third, the diagnoses

Table 3. Risk of Stroke Associated With Zolpidem Exposure[a]

Zolpidem Exposure	Comorbidity	OR (95% CI)	*P* Value[b]
Zolpidem exposure	Coronary artery disease		.0002
No	No	ref	
No	Yes	1.78 (1.69–1.88)	
Yes	No	1.63 (1.53–1.73)	
Yes	Yes	2.45 (2.31–2.60)	
Zolpidem exposure	Diabetes		< .0001
No	No	ref	
No	Yes	2.30 (2.18–2.43)	
Yes	No	1.68 (1.59–1.77)	
Yes	Yes	3.00 (2.80–3.22)	
Zolpidem exposure	Hypertension		< .0001
No	No	ref	
No	Yes	4.99 (4.71–5.30)	
Yes	No	2.20 (2.00–2.42)	
Yes	Yes	6.14 (5.75–6.57)	
Zolpidem exposure	Hyperlipidemia		< .0001
No	No	ref	
No	Yes	1.69 (1.61–1.78)	
Yes	No	1.76 (1.67–1.87)	
Yes	Yes	2.23 (2.10–2.38)	

[a]Model adjusted for age and gender.
[b]*P* value for interaction.
Abbreviation: ref = reference group.

in NHI claims primarily serve the purpose of administrative billing and do not undergo verification for scientific purposes. We were not able to contact the patients directly about their use of zolpidem because of the anonymity of their identification number. Prescriptions for these drugs before 1996 would not be captured in our analysis, which could have resulted in underestimation of the cumulative dosage and may weaken the observed association. However, the data on the prescription of zolpidem and stroke diagnosis were very reliable.

Several weak points in our study should be addressed. First, causality could not be established in this cross-sectional sample. We could not verify the exact temporal relationship between zolpidem use and stroke using our data. Second, there are a number of potentially confounding variables, including smoking, alcohol, body mass index, socioeconomic status, and family history, and they could have contributed to the use of zolpidem and/or stroke. The lack of the information on these factors was a major limitation of this study. In addition, the exposure to zolpidem independent of sleep disorder could be due to incomplete documentation in this database. Zolpidem use might be associated with other undocumented factors that were associated with its prescription.

CONCLUSIONS

This population-based, retrospective case-control study found that the use of zolpidem is significantly associated with increased risk for ischemic stroke, but not for hemorrhagic stroke. The increased risk may result from the effects of zolpidem outweighing the influence of any sleep disorder. Our findings require confirmation by a large, population-based, unbiased study before any firm conclusions can be drawn.

Drug names: zolpidem (Ambien, Edluar, and others).
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Additional information: The National Health Insurance Research Database can be found at http://nhird.nhri.org.tw/en/index.htm. The data, maintained by the National Health Research Institutes, Taiwan, are provided to scientists for research purposes.

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