An Increased Risk of Reversible Dementia May Occur After Zolpidem Derivative Use in the Elderly Population

A Population-Based Case-Control Study

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INTRODUCTION

Dementia is a clinical syndrome characterized by "a global deterioration of mental functioning in its cognitive, emotional, and cognitive aspects."[1] Dementia typically involves a long period of progressive decline in memory and other cognitive abilities secondary to brain dysfunction and is a major cause of disability in elderly people.[2] Alzheimer disease is the most common dementing disorder, followed by vascular dementia, frontal lobe dementia, and dementia with Lewy bodies. An expert panel estimated that the global prevalence of dementia is 3.9% in people over 60 years of age, and the estimated global annual incidence of dementia is approximately 7.5 per 1000 people.[3,4] The incidence of dementia ranges from approximately 1 per 100 person-years in people aged 60 to 64 years to >70 per 1000 person-years in people older than 90 years.[4] Because of an increased life expectancy in modern years, the number of people suffering from dementia has rapidly increased, potentially reaching up to 63 million people by 2030.[5]

The risk factors for dementia include an apolipoprotein E4 genotype, cardiovascular comorbidities, diabetes mellitus, cerebrovascular diseases, alcohol consumption, and a lower education level.[6]Benzodiazepine (BZD) and other non-selective γ-aminobutyric acid (GABA) agonists with hypnotic effects similar to those of zolpidem have been shown to disrupt the memory in both human participants and animal subjects.[7] The results of previous studies have suggested that BZDs are associated with an increased risk of dementia in the elderly population, and these risks decreased when BZD use is discontinued.[8–12] However, the possibility that zolpidem used independently of benzodiazepine derivatives, increases the risk for dementia has not been proposed.

Zolpidem and its derivatives (the Z drugs) are non-BZD hypnotic agent belonging to the imidazopyridine family. Zolpidem acts as an agonist of the benzodiazepine ω1 receptor component of the $GABA_A$ receptor complex and is commonly used in patients with insomnia, including elderly patients.[13] Zolpidem is well known for having a rapid onset (usually several minutes), short duration of action (the peak time is 2 hours, half time is 1.5–5.5 hours), low tolerance, and a low incidence of adverse effects in treating insomnia.[13,14]The most frequent adverse effects associated with zolpidem are nausea, headache, dizziness, drowsiness, hallucination, and short-term memory loss. A 3-week clinical trial revealed psychomotor retardation in 2% of patients receiving zolpidem and in 0% of patients in the placebo group.[15] However, there are limited clinical data concerning the effects of long-term zolpidem use on psychomotor or cognitive functions. Thus, the relationship between the use of zolpidem and the potential risk of developing dementia remains unknown. In the present study, we used a national population data bank to explore the associations between zolpidem and all dementia, non-Alzheimer disease dementia, and Alzheimer disease.

MATERIALS AND METHODS

Data Source

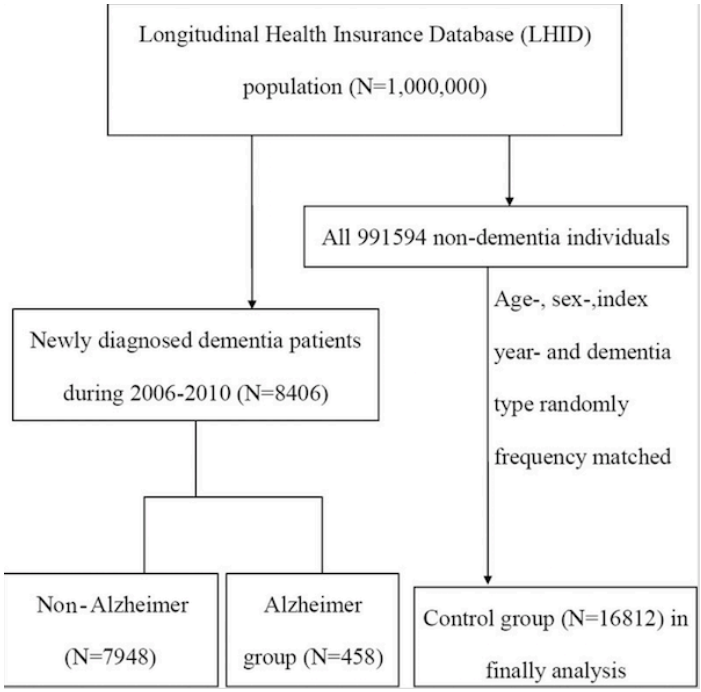
A case–control study was conducted using data from the Taiwan National Health Insurance Research Database (NHIRD). The Taiwan National Health Insurance Research Database (NHIRD) contains reimbursement claims data from the Taiwan National Health Insurance (NHI) system, which was established in 1996 and has provided coverage for approximately 99% of the population since 1998. The National Health Research Institute (NHRI) manages the annual claims data in the NHIRD, and the Longitudinal Health Insurance Database (LHID) was established for use in medical research. The demographic data, medications, treatments (including operations), and disease diagnoses (based on the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]) of patients are recorded in the NHIRD. The health facilities enrolled in the Taiwan NHI include local clinics, community

hospitals, regional hospitals, and medical centers. With the exception of some local clinics, the Taiwanese NHI includes almost all the primary, secondary, tertiary, and quaternary health care facilities in Taiwan. The LHID comprises historical claims data for 1 million patients randomly selected from the NHIRD. The NHRI encrypts the patients' personal information for privacy protection and provides researchers with anonymous identification numbers associated with the relevant claim information, which includes the patient's sex, date of birth, registry of medical services, and medication prescriptions. The patient consent is not required for accessing the NHIRD or LHID. This study was approved by the Institutional Review Board of China Medical University in central Taiwan (CMU-REC-101–012).

Study Design

A population-based case–control study was performed. Patients 65 years and older diagnosed with dementia (ICD-9-CM 290, 294) and Alzheimer disease (331.0) in 2006 to 2010 were defined as a case group. The patients with the diagnosis with Alzheimer disease were diagnosed by the board-certified neurologists and meet the following criteria: did not have history of severe trauma, stroke, or other neurology diseases that might interfere with the cognitive functions; have decreased score in Mini-Mental State Examination and Cognitive Ability Screening Instrument, complete blood sampling studies, and imaging studies. Patients with dementia diagnosis before 2006 were excluded. The flow chart in Figure Figure11demonstrates the selection process used in this study. The initial date of dementia diagnosis was set as the index date. The control group was selected from the people without dementia diagnosis in LHID observation and was 2-fold frequency matched according to sex, age (per 5 years), and index year. The major risk factor observed was zolpidem exposure. If the patients ever used zolpidem before index date, they were grouped into zolpidem used group. However, patients without zolpidem used before index date classified into non-zolpidem used group. The average zolpidem exposure dose was calculated by dividing the total zolpidem exposure (milligrams) according to the period between the first exposure and the index date (years). The average zolpidem exposure dose was separated into 3 groups according to the tertile.

FIGURE 1
The flow chart demonstrates the selection process used in this study.



Other dementia-associated comorbidities were also considered potential confounding factors to determine associations between dementia and zolpidem. Data for the underlying comorbidities, including hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), coronary artery disease (CAD) (ICD-9-CM 410–414), stroke (ICD-9-CM 430–438), hyperlipidemia (ICD-9-CM 272), depression (ICD-9-CM 296.2–296.3 and 300.4), and anxiety (ICD-9-CM 300.0, 300.2, 300.3, 308.3, and 309.81), were collected before the index date.

Drugs potentially associated with the development of dementia, including anti-hypertension agents such as calcium channel blockers (Anatomical Therapeutic Chemical [ATC] code: C08), beta-blockers (ATC code: C07), alpha-blockers (ATC code: C02), diuretics (ATC code: C03), angiotensin-converting enzyme antagonists (ACEI), angiotensin receptor blockers (ARB) (ATC code: C09), and anticholesterol statin drugs (ATC code: C10) benzodiazepine (ATC code: N05), and similar derivative drugs that were available such as zopiclone (ATC code: N05) were analyzed. We also considered effect of anti-psychotic drug used (first generation antipsychotics and second generation antipsychotics) and anti-depression drug used (including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, heterocyclic antidepressants, and others [bupropion, venlafaxine, mirtazapine, and duloxetine]). All of these drug definitions were considered the drug use group as the patients at least once use before the index date.

Statistical Analysis

The distribution of the study population, which was based on the demographic characteristics and the disease history data, was analyzed. The χ^2 test was used for categorical variables, and Student *t* test was used for continuous variables to evaluate the differences among the study groups. The odds ratio (OR) and 95% confidence interval (95% CI) were measured for each comparison to estimate the associations between zolpidem use and dementia using logistic regression. Adjusted odds ratios (AORs) were also determined after adjusting for potential confounders. To evaluate the dose response of the association between the average zolpidem dose and dementia, logistic regression was used, and the average zolpidem dose was treated as a continuous variable across a range of average doses to evaluate trends in dementia diagnosis. We tested the multiplicative interaction of zolpidem use and each comorbidities (or drugs) by logistic regression and presented the effect of zolpidem for dementia under the different level of each comorbidities (or drugs). All data management and statistical analyses were performed using the SAS 9.1.3 software (SAS Institute, Cary, NC). All statistical tests were 2-sided, and *P* values <0.05 were considered statistically significant.

RESULTS

A total of 8406 dementia patient files were identified, and the control group consisted of 16,812 patients. The demographic characteristics of the study population are presented in Table Table1.1. Comparing with the control group, the dementia patients have longer zolpidem exposure time (302.8 days vs 345.1 days, $P=0.001$) and higher exposure dose, were more likely to have been exposed to zolpidem (44.8% vs 30%, $P<0.0001$), zopiclone (20.3% vs 12.9%, $P<0.0001$), and BZDs (91.3% vs 83.6%, $P<0.0001$), to have received simultaneous treatments with anti-hypertension agents (79.8% vs 70.3%, $P<0.0001$) and anti-cholesterol statin agents (26.3% vs 22%, $P<0.0001$), and to have had underlying diseases, such as hypertension (81.6% vs 72.6%, $P<0.0001$), diabetes (32.2% vs 24.1%, $P<0.0001$), stroke (28.3% vs 12.2%, $P<0.0001$), CAD (51% vs 42%, $P<0.0001$), hyperlipidemia (41.2% vs 36%, $P<0.0001$), depression (17.1% vs 6.3%, $P<0.0001$), and anxiety disorder (27.4% vs 17.9%, $P<0.0001$).

TABLE 1
Demographic Status and Comorbidity Compared Between Control Group and Dementia Group

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TABLE 1

Demographic Status and Comorbidity Compared Between Control Group and Dementia Group

Variable	Control Group, N = 16812 (%)	Dementia Group, N = 8406 (%)	*P*
Age, years (SD)			>0.99
65–74	5030 (29.9)	2515 (29.9)	
75–84	8244 (49.0)	4122 (49.0)	
≥85	3538 (21.0)	1769 (21.0)	
Sex			>0.99
Female	8886 (52.9)	4443 (52.9)	
Male	7926 (47.1)	3963 (47.1)	
Zolpidem exposure			<0.0001
No	11770 (70.0)	4640 (55.2)	
Yes	5042 (30.0)	3766 (44.8)	
Zolpidem average exposure (mg/year)			<0.0001
None	11770 (70.0)	4640 (55.2)	
<170	2721 (16.2)	1656 (19.7)	
170-819	1196 (7.1)	1034 (12.3)	
≥820	1125 (6.7)	1076 (12.8)	
Mean (SD)	302.8 (587.4)	345.1 (605.0)	0.0010
Median (IQR)	60 (263)	84 (330)	<0.0001
BZD drug used	14056 (83.6)	7677 (91.3)	<0.0001
Zopiclone used	2165 (12.9)	1710 (20.3)	<0.0001
Anti-hypertension drugs used	11815 (70.3)	6711 (79.8)	<0.0001
Statin used	3699 (22.0)	2208 (26.3)	<0.0001
Anti-psychotic drugs used	5144 (30.6)	3967 (47.2)	<0.0001
Anti-depression drugs used	6147 (36.6)	4504 (53.6)	<0.0001
Comorbidity			
Hypertension	12213 (72.6)	6858 (81.6)	<0.0001
Diabetes	4052 (24.1)	2710 (32.2)	<0.0001
Stroke	2054 (12.2)	2382 (28.3)	<0.0001
CAD	7057 (42.0)	4287 (51.0)	<0.0001
Hyperlipidemia	6053 (36.0)	3465 (41.2)	<0.0001
Depression	1065 (6.3)	1439 (17.1)	<0.0001
Anxiety	3005 (17.9)	2300 (27.4)	<0.0001

BZD = benzodiazepine, CAD = coronary artery disease, IQR = interquartile range, SD = standard deviation.

The logistic regression models were adjusted for potential confounders, such as age, sex, CAD, diabetes, stroke, hyperlipidemia, depression, anxiety, and the use of antihypertension agents, anticholesterol statin agents zopiclone and BZD drug uses, to evaluate the relationship between zolpidem use and dementia (Table (Table2).2). Zolpidem use and dementia remained significantly associated (dementia: AOR=1.33, 95% CI 1.24–1.41; $P<0.0001$; non-Alzheimer disease dementia: AOR=1.33, 95% CI 1.25–1.42; $P<0.0001$), although the relationship effects between the zolpidem use and Alzheimer disease were not significant (Alzheimer disease: AOR=1.17, 95% CI 0.90–1.54, $P=0.2410$).

TABLE 2

Effects of Zolpidem Exposure on Dementia in Individuals in Different Average Cumulative Exposure Doses

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TABLE 2

Effects of Zolpidem Exposure on Dementia in Individuals in Different Average Cumulative Exposure Doses

Variable	All Study Population*							Non-Alzheimer Disease Dementia†							Alzheimer Disease Only‡						
	Zolpidem Exposure			Zolpidem Average Exposure, mg/year				Zolpidem exposure			Zolpidem Average Exposure, mg/year				Zolpidem Exposure			Zolpidem Average Exposure, mg/year			
	No	Yes	None	<170	170–819	≧820	*P* Value for Trend	No	Yes	None	<170	170–819	≧820	*P* Value for Trend	No	Yes	None	<170	170–819	≧820	*P* Value for Trend
Crude OR (95% CI)	Ref	1.89 (1.79–2.00)	Ref	1.54 (1.44–1.66)	2.19 (2.00–2.40)	2.43 (2.22–2.66)	<0.0001	Ref	1.93 (1.82–2.04)	Ref	1.57 (1.46–1.69)	2.21 (2.02–2.43)	2.49 (2.27–2.74)	<0.0001	Ref	1.41 (1.11–1.78)	Ref	1.09 (0.79–1.52)	1.91 (1.29–2.83)	1.55 (1.06–2.27)	0.0010
P		<0.0001		<0.0001	<0.0001	<0.0001					<0.0001	<0.0001	<0.0001			0.0048		0.5903	0.0013	0.0233	
Adjusted OR (95% CI)	Ref	1.33 (1.24–1.41)	Ref	1.18 (1.1–1.28)	1.50 (1.36–1.65)	1.52 (1.38–1.68)	<0.0001	Ref	1.33 (1.25–1.42)	Ref	1.20 (1.11–1.29)	1.49 (1.34–1.65)	1.55 (1.39–1.72)	<0.0001	Ref	1.17 (0.90–1.54)	Ref	0.97 (0.68–1.37)	1.65 (1.08–2.51)	1.18 (0.78–1.78)	0.1238
P		<0.0001		<0.0001	<0.0001	<0.0001			<0.0001		<0.0001	<0.0001	<0.0001			0.2410		0.8509	0.0199	0.4413	

CI = confidence interval, OR = odds ratio. †Model: adjusted for age, sex, CAD, diabetes, anti-hypertension drugs, stroke, statin, depression, anxiety, Zopiclone, and BZD used.
*All study population (case/control: 8406/16812).
†Dementia except Alzheimer disease (case/control: 7948/15896).
‡Alzheimer only (case/control: 458/916).

The average cumulative zolpidem doses were analyzed to identify dose effects. Zolpidem use still has significant dose–response effects for most of types of dementia except Alzheimer disease (dementia: <170 mg/y [AOR = 1.18, 95% CI 1.11–1.28], 170–819 mg/y [AOR = 1.50, 95% CI 1.36–1.65], ≧820 mg/y [AOR = 1.52, 95% CI 1.38–1.68], *P* value for trend <0.001; non-Alzheimer disease dementia: <170 mg/y [AOR = 1.20, 95% CI 1.11–1.29], 170–819 mg/y [AOR = 1.49, 95% CI 1.34–1.65], ≧820 mg/y [AOR = 1.55, 95% CI 1.39–1.72], *P* value for trend <0.001; and Alzheimer disease: <170 mg/y [AOR = 0.97, 95% CI 0.68–1.37], 170–819 mg/y [AOR = 1.65, 95% CI 1.08–2.51], ≧820 mg/y [AOR = 1.15, 95% CI 0.78–1.78], *P* value for trend = 0.4413).

Potential modifying effects for comorbidities that might interfere with the association between dementia and zolpidem were analyzed (Table (Table3).3). Of the patients with zolpidem exposure, although effect modifiers such as hypertension, diabetes, stroke, CAD, hyperlipidemia, and anxiety, depression, anti-psychotic agent, and anti-depressant use had positive effects for dementia (hypertension: AOR = 1.72, 95% CI 1.62–1.83; diabetes: AOR = 1.64, 95% CI 1.48–1.81; stroke: AOR = 1.39, 95% CI 1.23–1.57; CAD: AOR = 1.74, 95% CI 1.61–1.88; hyperlipidemia: AOR = 1.74, 95% CI 1.60–1.90; anxiety: AOR = 1.66, 95% CI 1.48–1.86; depression: AOR = 1.37, 95% CI 1.15–1.63), zolpidem exposure alone also has more positive effects on dementia in most circumstances (non-hypertension: AOR = 2.30, 95% CI 2.01–2.62; non-diabetes: AOR = 1.95, 95% CI 1.83–2.08; non-stroke: AOR = 1.88, 95% CI 1.76–2.00; non-CAD: AOR = 1.88, 95% CI 1.76–2.00; non-hyperlipidemia: AOR = 1.95, 95% CI 1.82–2.10; non-statin: AOR = 1.92, 95% CI 1.80–2.04; non-BZD: AOR = 1.96, 95% CI 1.49–2.59; non-anxiety: AOR = 1.76, 95% CI 1.65–1.88; non-depression: AOR = 1.68, 95% CI 1.58–1.78). Patients receiving zolpidem with anti-psychotic or anti-depressant agents at the same time had more positive effects on dementia risk (anti-psychotic agents vs non-antipsychotic agents: AOR = 1.75 [95% CI 1.61–1.90] vs. 1.57 [95% CI 1.46–1.70]; anti-depressant vs non-antidepressant agents: AOR = 1.66 [95% CI 1.54–1.80] vs 1.54 [95% CI 1.42–1.68]). Although large numbers of patients were co-prescribed zolpidem and BZD derivatives, the effects of interactions between zolpidem and BZD derivatives were not significant.

TABLE 3

Interactions Between Zolpidem Exposure and Comorbidities That Were Associated With Dementia Risk

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TABLE 3

Interactions Between Zolpidem Exposure and Comorbidities That Were Associated With Dementia Risk

	Zolpidem Exposure			
Status	**Control Group, n (%)**	**Dementia group, n (%)**	**OR (95% CI)**	***P* Value for Interaction**
Hypertension				<0.001
No	794 (17.3)	496 (32.0)	2.30 (2.01–2.62)	
Yes	4248 (34.8)	3270 (47.7)	1.72 (1.62–1.83)	
Anti-hypertension drugs				0.0006
No	861 (17.2)	528 (31.2)	2.20 (1.94–2.50)	
Yes	4181 (35.4)	3238 (48.3)	1.71 (1.61–1.82)	
Diabetes				0.005
No	3497 (27.4)	2408 (42.3)	1.95 (1.83–2.08)	
Yes	1545 (38.1)	1358 (50.1)	1.64 (1.48–1.81)	
Stroke				<0.001
No	4177 (28.3)	2566 (42.6)	1.88 (1.76–2.00)	
Yes	865 (42.1)	1200 (50.4)	1.39 (1.23–1.57)	
CAD				0.207
No	2247 (23.0)	1479 (35.9)	1.89 (1.75–2.05)	
Yes	2795 (39.6)	2287 (53.4)	1.74 (1.61–1.88)	
Hyperlipidemia				0.061
No	2711 (25.2)	1957 (39.6)	1.95 (1.82–2.10)	
Yes	2331 (38.5)	1809 (52.2)	1.74 (1.60–1.90)	
Statin				0.1523
No	3529 (26.9)	2560 (41.3)	1.92 (1.80–2.04)	
Yes	1513 (40.9)	1206 (54.6)	1.75 (1.58–1.95)	
BZD used				0.428
No	172 (6.2)	84 (11.5)	1.96 (1.49–2.59)	
Yes	4870 (34.7)	3682 (48.0)	1.75 (1.65–1.85)	
Anxiety				0.398
No	3310 (24.0)	2174 (35.6)	1.76 (1.65–1.88)	
Yes	1732 (57.6)	1592 (69.2)	1.66 (1.48–1.86)	
Depression				0.059
No	4327 (27.5)	2702 (38.8)	1.68 (1.58–1.78)	
Yes	715 (67.1)	1064 (73.9)	1.37 (1.15–1.63)	
Anti-psychotic drug used				0.085
No	2734 (23.4)	1444 (32.5)	1.57 (1.46–1.70)	
Yes	2308 (44.8)	2322 (58.5)	1.75 (1.61–1.90)	
Anti-depression drug used				0.155
No	2199 (20.6)	1115 (28.6)	1.54 (1.42–1.68)	
Yes	2843 (46.3)	2651 (58.9)	1.66 (1.54–1.80)	
Zopiclone used				0.073
No	3634 (24.8)	2493 (37.2)	1.81 (1.70–1.93)	
Yes	1408 (65.0)	1273 (74.4)	1.56 (1.36–1.80)	

Model adjusted for age and sex. BZD = benzodiazepine, CAD = coronary artery disease, CI = confidence interval, OR = odds ratio.

DISCUSSION

The present population-based case–control study suggests that zolpidem' use might increase the risk of developing dementia in the elderly population. The accumulative dose of zolpidem, alone, or with other underlying diseases, such as hypertension, diabetes, and stroke, was significantly associated with dementia after controlling for potential confounders, such as age, sex, CAD, diabetes, antihypertension drugs, stroke, anticholesterol statin drugs, depression, anxiety, and BZD use; however, the effects of zolpidem on patients with Alzheimer disease remained obscure. The adjusted odds ratio for patients whose cumulative exposure doses were between 170 and 819 mg/year (adjusted OR: 1.65, 95% CI 1.08–2.51, P=0.0199) was significant; however, the effects for lower and higher cumulative dose were not significant.

The etiology for dementia is complex.[16,17] Alzheimer disease is the leading subtype of dementia and has been identified as a protein degenerative disease that is primarily caused by the accumulation of abnormally folded amyloid beta and phosphorylated tau proteins in the brain.[18,19] Clinical presentations, histories, neurological examinations, images, and biomarkers are required to diagnose Alzheimer disease. Dementias other than Alzheimer disease (non-Alzheimer dementias) comprise heterogeneous diseases, including

vascular dementia, mixed dementia, Parkinson disease, dementia with Lewy bodies, Huntington disease, Creutzfeldt–Jakob disease, and frontotemporal dementia/Pick disease.[16] Interactions between other factors, such as hypercholesterolemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, diabetes, and sleep deprivation or sleep fragmentation, were reported to be risk factors that might contribute to dementia.[19–21] However, few studies have addressed the potential long-term psychoneurological effects of drugs on non-Alzheimer dementia or Alzheimer disease.[8,9,22–24]

Zolpidem is an effective non-BZD drug that is primarily used for treating insomnia in the elderly population.[25,26] Previous clinical trials have demonstrated the effects of zolpidem on the central nervous system (eg, confusion, impaired cognitive and motor function, postural sway, and ataxia), and an increased risk of falling has also been observed.[27–29] Zolpidem has also been shown to disrupt memory in human patients and animal subjects.[7] Comparable dose-related impairment was also observed in healthy participants asked to perform cognitive-related tests, such as picture recall, digit entry and recall, a digit symbol substitution test, repeated acquisition and circular lights tasks, and balance tests.[30] The cognition-impairing effects in executive function tasks were characterized in animal models before. Previous study results suggested that zolpidem displays a high affinity for α1 subunit of $GABA_A$ receptors; therefore, the drug impairs the human cognitive domain in the prefrontal cortical areas, which are involved in processes such as goal forming, planning, initiation, preservation and alteration of goal-directed behaviors, problem-solving, response inhibition, and cognitive flexibility.[31,32] Because the aging brain has increased α1 subunit of $GABA_A$ receptor–binding sites and α1 subunit of $GABA_A$ receptor mRNA levels, the cognition-impairing effects of zolpidem might reflect the elderly population's increased risk of developing non-Alzheimer dementia.[33,34] In contrast, the α1 subunit of $GABA_A$ receptor protein and mRNA levels were reduced in the brain cortex regions of Alzheimer disease patients.[35,36] The different compositions indicate that increases or decreases in the proportion of receptors containing a particular α subunit may reflect the affinity of the receptor for zolpidem, resulting in altered drug responses between patients of non-Alzheimer dementias and Alzheimer disease in the elderly population.

Whether cognitive effects on zolpidem could extend to other Z drugs still remain obscure. Previous studies suggested zaleplon had a rapid elimination and had fewer residual side effects after taking a single dose at bedtime. By comparison, zolpidem and zopiclone have a more delayed elimination than zaleplon. The differences in potency based on plasma concentrations suggested that there are differences in binding to the GABA receptor complex. For example, zopiclone interacts with both benzodiazepine ω1and ω2 $GABA_A$receptors, and zolpidem mainly acts on benzodiazepine ω1 $GABA_A$ receptors.[37] Therefore, there may be a prolonged drug effect and result in residual sedation and side effects. The Z drugs undergoes hepatic metabolism by cytochrome P450.[14] The delayed clearances of the Z drugs were significantly decreased in patients with preexisting advanced liver diseases. Furthermore, variations in genetic polymorphism of the cytochrome P450 in different population might result in different responses as well. A study has suggested that the CYP3A4 and CYP2C19 genetic polymorphisms are associated with the poor metabolism of zolpidem in the Chinese Han population.[38]

A limited number of human studies have explored the relationship between neuropsychological drugs and the development of dementia or Alzheimer disease. A meta-analysis setting out to ascertain which domains of cognitive function were influenced among the Z drugs indicated very few studies evaluate the individual cognitive effects of the Z drugs. Most of the studies focused on the next-day residual cognitive effects of the Z drugs following nocturnal administration.[39] The Z drugs have been heralded as a new frontier with consistent increase in the prescription in the pharmacological treatments available for insomnia patients due to the adverse and deleterious effects associated with long-term benzodiazepine use. There needs to be more thorough investigations into the possible effects on the daily functioning of individuals who take these medications. The results of the present study indicate the potential associations regarding the cumulative dose and interactions among commonly prescribed tranquilizers, zolpidem, underlying comorbidities, and the development of dementia or Alzheimer disease in the elderly population. Although detailed observations and medical records were not obtained and effect modifiers and confounders were not completely controlled, correlations between zolpidem and dementia in the elderly population were observed.

LIMITATIONS

The limitations of the present study include the limitations of the clinical data collected from the NHIRD, the difficulty associated with controlling for confounding factors in a retrospective study design, and the incomplete verification of the data in the NHIRD. The NHIRD does not provide detailed information regarding smoking habits, alcohol consumption, substance use, body mass index, physical activity, socioeconomic status, family history, and detailed medical records such as sleep quality records, reasons for zolpidem withdrawal, or intermittent used, which are potential confounding factors for this analysis.[9]Furthermore, some patients in control group might present prodromal symptoms like nxiety, depression, or insomnia before dementia diagnosis was made and led to misclassification and selection bias. The registries in the NHI claims system were primarily designed for administrative billing, and the registry data are not subjected to the stringent levels of verification appropriate for many types of scientific research. There was also no method for directly contacting the patients to obtain additional information on the use of zolpidem because the participants remained anonymous. However, the data from the NHIRD regarding prescriptions and the diagnosis of major underlying diseases and dementia are highly reliable. Qualified neurologists performed a series of neurological examinations. Because of the limitations of the NHIRD, the prescription records for zolpidem before 1996 were not acquired for analysis; therefore, shorter follow-up examinations and lower cumulative doses for zolpidem were calculated, and the risk associations between zolpidem and dementia might also be underestimated. Future studies, such as population-based unbiased randomized observational trials, are warranted to confirm the causal relationships between zolpidem use and dementia.

In conclusion, zolpidem use might be associated with an increased risk for dementia in the elderly population. An increased accumulative dose might result in a significantly higher risk to develop dementia in patients with underlying diseases, such as hypertension, diabetes, and stroke. The long-term effects of zolpidem on patients with Alzheimer disease might not be significant in the elderly population. Therefore, the careful evaluation of the indications of zolpidem use and close follow-up examinations of the cognitive status of elderly patients receiving zolpidem are essential.