The Association Between the Use of Zolpidem and the Risk of Alzheimer's Disease Among Older People

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OBJECTIVES: To evaluate the association between zolpidem use and the risk of Alzheimer's disease among older people.

DESIGN: A retrospective cohort study using data from 2001 to 2011 from the National Health Insurance Research Database.

SETTING: Taiwan.

PARTICIPANTS: A total of 6,922 patients aged 65 years or older enrolled from January 2002 to December 2004 (the enrollment period).

INTERVENTION (EXPOSURE): Zolpidem users were identified as patients who used zolpidem during the enrollment period. The index date was the date of the first zolpidem prescription. Dosage of zolpidem use was defined using cumulative defined daily dose (cDDD) based on the cumulative dosage that patients took within one year after the index date (grouped as: less than 28, 28–90, 91–180, and more than 180 cDDD).

MEASUREMENTS: The occurrence of Alzheimer's disease was defined as the time period from the end of one year after the index date to the date of the Alzheimer's disease diagnosis. The propensity score was used to adjust the measured confounders of Alzheimer's disease. Cox proportional hazards models were used to evaluate the association between zolpidem use and the incidence of Alzheimer's disease.

RESULTS: Zolpidem users with a high cumulative dose (>180 cDDD) in the first year after initiation had a significantly greater risk of Alzheimer's disease than non-zolpidem users (HR = 2.97, 95% CI = 1.61–5.49) and low cumulative dose (<28 cDDD) users (HR = 4.18, 95% CI = 1.77–9.86).

CONCLUSION: We found the use of a high cumulative dose of zolpidem was associated with an increased risk of Alzheimer's disease among older people living in Taiwan. It is advised to use caution when considering long-term use of zolpidem in older patients. **J Am Geriatr Soc 65:2488–2495, 2017.**

Key words: zolpidem; Alzheimer's disease; hypnotics; National Health Insurance Research Database (NHIRD); Taiwan

Dementia is a global health burden.[1,2] According to a recent report in 2015 from the World Health Organization, there are 47.5 million people living with dementia worldwide, and over 60% of dementia cases are caused by Alzheimer's disease (AD).[3] With a global aging population, the total number of people with AD or dementia is expected to significantly increase over the next 10 years.[4–6] In 2010, the total global cost of dementia was $604 billion, and the amount will increase by 85% between 2010 and 2030.[7]

Zolpidem, a non-benzodiazepine hypnotic, is often used for short-term treatment of insomnia.[8–11] It remains one of the most commonly prescribed hypnotics due to the advantages of quick onset and little residual effects.[10–12] The pharmacologic mechanisms of zolpidem, which include anxiolytic, muscle relaxant, sedative, and anticonvulsant effects were found to work throughα1, 2, 3 and 5 subunits of gamma-amino-butyric acid type A (GABAA) receptors.[13] Unlike benzodiazepines, zolpidem has high-affinity binding to the α1 subunit, which provides more specific sedative properties than benzodiazepines.[13]

Previous studies reported that both benzodiazepine and zolpidem use are associated with memory loss and a decline in the cognitive function.[14,15] A link between benzodiazepine use and dementia is well documented.[16–19]

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Benzodiazepines inhibit neurotransmitters in the brain through acting on receptors of γ aminobutyric acid A and have been hypothesized to increase the development of AD.[17] Although zolpidem has fewer benzodiazepine-like adverse effects, taking zolpidem may still be associated with an increased risk of cognitive and psychomotor decline, eventually resulting in a long-term memory loss.[4]

A limited number of studies have investigated the association between zolpidem use and dementia. A recent case-control study reported that zolpidem use was associated with an increased risk of dementia.[20] Studies have reported the association between the cumulative dose-response of benzodiazepines use and the risk of dementia or AD.[21] Whether zolpidem use has the same dose-response effects, as benzodiazepine requires further investigation. It also remains unclear whether zolpidem use is associated with an increased risk of developing AD. Therefore, the purpose of this study was to evaluate the association between zolpidem use and the risk of AD among older patients in Taiwan. We hypothesized that zolpidem users would have a higher risk of being diagnosed with AD than non-zolpidem users. Furthermore, we hypothesized that higher cumulative doses of zolpidem use would have a greater association with being diagnosed with AD compared to lower cumulative dose or not having been exposed to zolpidem at all.

METHODS

Data Source

This was a retrospective cohort study based on data from the National Health Insurance Research Database (NHIRD). A single-payer National Health Insurance (NHI) program was implemented in Taiwan in 1995, and currently up to 99.9% of the 23 million Taiwanese residents are enrolled in this program.[22–24] The NHIRD, which is an administrative claims database containing registration files, patient identification files, and medical claims files (including inpatient records, ambulatory care records, and prescription files), is generated by the National Health Insurance Administration and regularly maintained by the Taiwan National Health Research Institutes.[22–24] We used the 2010 Longitudinal Health Insurance Database (LHID 2010), which contains data of one million Taiwanese beneficiaries in 2010 randomly selected from the NHIRD.[22–24] Overall, 11 years of data were included, from January 1, 2001 to December 31, 2011.

Study Population and Study Design

We defined the enrollment period from January 1, 2002 to December 31, 2004 to select patients who were aged 65 years or older. We used the new user design to conduct this study. To be considered new users, patients had to have had at least one prescription of zolpidem during the enrollment period and the initial prescription (the first prescription) needed to have been written for a quantity equal to at least a seven-day supply. The date of the first zolpidem prescription was defined as the index date. Zolpidem users were further required to be free of zolpidem or other non-BZD drugs (including zolpiclone, zaleplon, and eszopiclone) for one year before the index date (i.e., pre-index period). Patients who were not qualified as users of zolpidem were considered non-zolpidem users.

We further excluded patients if they had ever been diagnosed with AD (the International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM] code, 331.0) or any other type of dementia (290.0, 290.1, 290.2, 290.3, 290.4, 294.1, 331.1, 331.2) at the index date or during the pre-index period. Patients with any records of cognitive impairment (331.8, 331.83, and 331.9), Huntington's disease (333.4), and Creutzfeldt–Jakob disease (046.11, 046.19) at the pre-index period were excluded. Moreover, patients with any medication treatment for dementia (donepezil, rivastigmine, galantamine, and memantine) on the index date or in the pre-index period were excluded.

The follow-up period started on one year after the index date to account for the induction period and continued for 6 years. Considering that Alzheimer's disease is a progressive degenerative disease and that the effect of zolpidem may require a period of time to manifest, a one-year induction period after the index date was set to prevent a reverse causality bias. Figure 1 showed the details of the enrollment process.

Exposure

The primary exposure was the use of zolpidem, defined as at least one zolpidem prescription written for a minimum supply to cover seven days of consecutive zolpidem prescription filled since the index date. Using the rule of having a minimum of seven-day supply of drug was to prevent misassigning patients who used zolpidem only occasionally or a few days to be classified as zolpidem users. Overall, patients were categorized into two groups as follows:

(1) Zolpidem users: patients with at least one prescription written for a quantity of a minimum of seven-day supply. The initial prescription that met this criteria was considered the index prescription and the date it was dispensed was considered the index date.
(2) Non-zolpidem users: patients without any zolpidem prescription records or who received zolpidem prescriptions written for a quantity smaller than a seven-day supply during the induction period.

Each zolpidem user was matched up to one non-user on age and sex. The matched nonusers were assigned the same index date as the new user of zolpidem. Non-users were also required to be free of zolpidem or other non-BZD drugs during the pre-index period to avoid bias from the prevalent users.

We also studied the cumulative exposure of zolpidem use, which was measured in the unit of defined daily dose (DDD) that has been recommended by WHO.[25] The DDD was defined as the average maintenance dose of a medication per day for the major indication in one adult.[25] The DDD of zolpidem was 10 mg. To obtain the cumulative DDD (cDDD) for each patient, we summed all the zolpidem doses prescribed during a defined period (i.e., one year after index date) and then convert the quantity to the

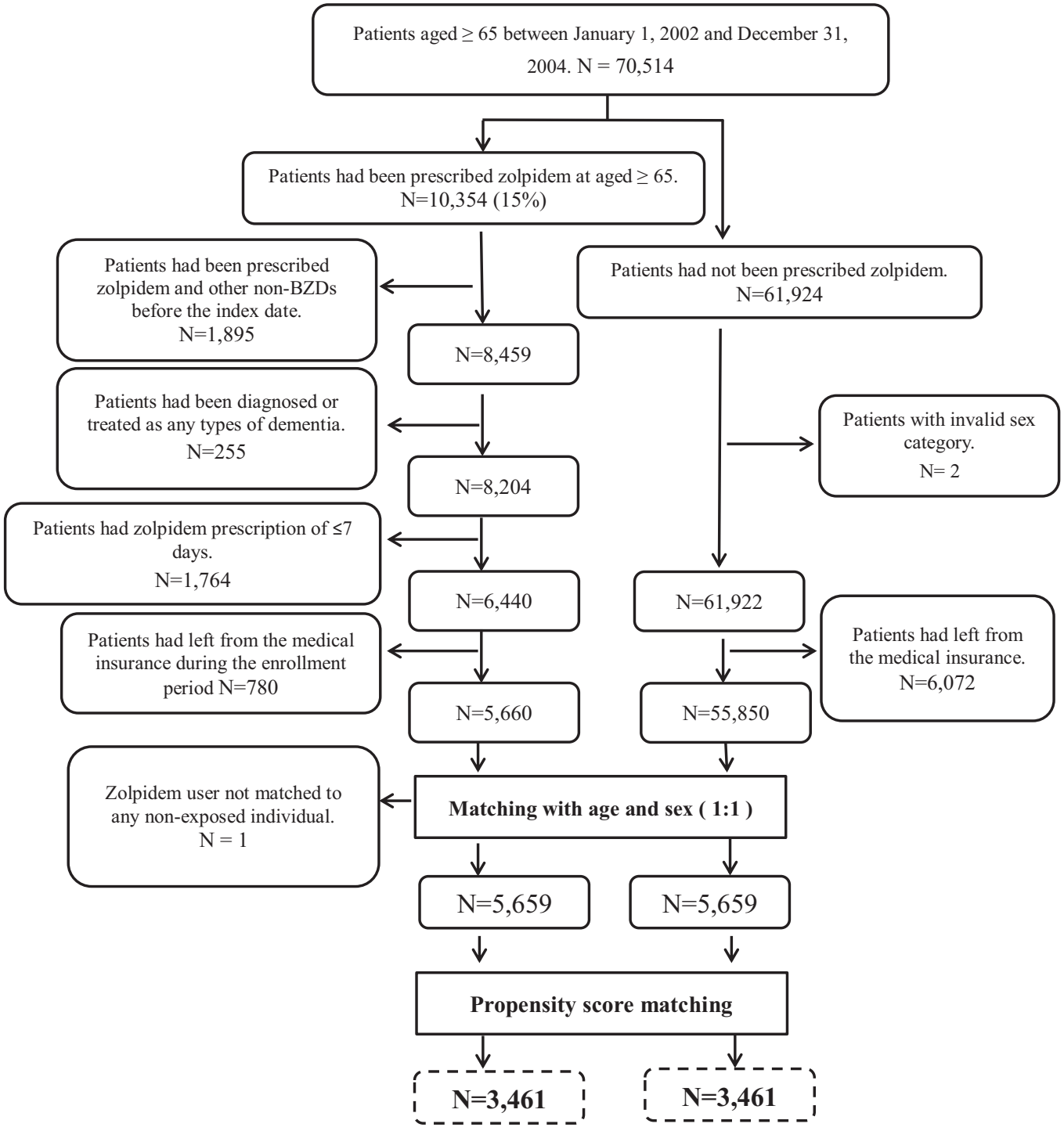

Figure 1. The identification process of the study population and the classification of zolpidem and non-zolpidem users.

number of DDD.[26] According to the cDDD of zolpidem during the exposure period, all the zolpidem users were categorized into four groups: less than 28, 28–90, 91–180, and more than 180 cDDD.

Study Outcomes

The outcome was the occurrence of AD, which was defined as the time to the first diagnosis of AD (331.0). The diagnosis was restricted to be made by a neurologist or a psychiatrist to ensure the validity of the diagnosis. It was measured from the end of the induction period to the date of the AD diagnosis or to the date of censoring. Patients with a prior diagnosis of AD were excluded. Patients were censored at the earliest date of insurance withdrawal, death, or the end of the six-year follow-up period. All the diagnoses of AD were measured in the six years after the induction period in two groups.

Covariates

In addition to age and sex, covariates included condition-related variables and medication-related variables. Condition-related variables included hypertension (401.0, 401.1, 401.9, 402.0, 402.1, 402.9, 403.0, 403.1, 403.9, 404.0, 404.1, and 404.9), stroke (431, 432.0, 432.1, 432.9,433, 434, 436, and 437), myocardial infarction (410 and 412), hypercholesterolemia (272.0), diabetes mellitus (250), depression (296.2, 296.3, 300.4, and 311), anxiety (300), psychotic-related disorder (295, 297, and 298), alcohol-related disorder (291, 303, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, and 571.3), sleep disorder (307.4 and 780.5), Parkinson's disease (332.0) and head injury (800–804, 850–854, and 959.01).[21,27–29] The above conditions were included because previous studies have reported that these conditions were potential risk factors for the development of AD.[21,27–29] Medication-related variables included drug classes of antihypertensive drugs, anti-diabetic medication, anticoagulants, anti-hyperlipidemia drugs, antidepressants, benzodiazepines (BZDs), anti-Parkinson medication and antipsychotics. All covariates were identified during the pre-index period. In addition, we further included mental health-related physician visits as one additional covariate because mental illnesses were considered to have a high association with the development of AD.[30,31] We calculated the total number of outpatient and emergency visits for neurology and psychiatry clinics in the pre-index period. The variable was categorized into 4 groups by the number of the visits (less than 6, 6–10, 11–15, and more than 15 visits).

Statistical Analysis

Propensity score matching was used to balance the measurable confounders between zolpidem users and non-zolpidem users.[32,33] For each patient, we estimated the probability of receiving zolpidem (i.e., the propensity score, PS), using a logistic regression model including all variables presented in the previous section. We then used a greedy 5-to-1 digit matching algorithm without replacement to match each zolpidem user with one nonuser of zolpidem on the propensity score.[33] The matching process started with the first 5 significant figures of the propensity score, moved to the first 4 significant figures, and so forth. Zolpidem users who had no match to at least 1 decimal place were excluded. Matching helped to minimize the likelihood that any differences in patient outcome observed were due to the zolpidem use other than confounders. The baseline characteristics of the study population before and after propensity score matching were described with descriptive statistics. The Student's *t*-test and chi-square test were used to compare patient characteristics. Time to event analysis was performed using the Cox proportional hazards model to estimate the relative hazards of AD comparing zolpidem users to nonusers.

Sensitivity analysis

We further conducted two sensitivity analyses. The first sensitivity analysis was to vary the length of the exposure period from one year to two years to take into account the effect of the longer zolpidem exposure. Both groups were followed five years after the two-year exposure period. The cumulative dose of the zolpidem use was calculated during the two-year exposure period. In addition, the second sensitivity analysis was to include the AD diagnosis given by any practitioners instead of the diagnosis only given by a psychiatrist or neurologist in the main analysis.

SAS® proprietary Software, Release 9.3 (SAS institute Inc., Cary, NC)[34] was used for all the analysis in this study. A two-sided *P* value ($P < .05$) was used to determine statistical significance. This study was reviewed and approved by the Taipei Medical University Joint Institutional Review Board (TMU-JRIB) in May 2015.

RESULTS

Table 1 shows the baseline characteristics of the study population before and after propensity score matching. A total of 11,318 patients were identified before matching. The mean age of the study population was 72.1 years old and 62.1% patients were female. More zolpidem users had the diagnoses of hypertension, stroke, myocardial infarction, hypercholesterolemia, diabetes mellitus, depression, anxiety, psychotic-related disorder, alcohol-related disorder, sleep disorder, Parkinson's disease, and head injury. Moreover, a significantly higher proportion of zolpidem users used other medications when compared with non-zolpidem users. After propensity score matching, there were 3,461 zolpidem users and 3,461 non-users. All the covariates except the use of anti-Parkinson medication ($P < .05$) were balanced between the two groups.

Table 2 shows the incident rates and follow-up time among the study population. During the six-year follow-up period, 75 patients developed AD, which included 43 (1.2%) patients among the zolpidem users and 32 (0.9%) among the non-zolpidem users. Among zolpidem users, 71% (2,457) of the users took zolpidem under 90 cDDD during the first year following the index date (35.2%, <28 cDDD and 35.8%, 28–90 cDDD). About 16% (553) of the users were in the >180 cDDD group. The six-year incidence of developing AD among zolpidem users was 0.7% for the <28 cDDD group, 1.2% for the 28–90 cDDD group, 1.1% for the 91–180 cDDD group, and 2.7% for the >180 cDDD group. The mean follow-up time was 5.97 years for zolpidem users and 5.98 years for non-zolpidem users.

Table 3 shows the results of the Cox proportional hazards regression model. The risk of developing AD for zolpidem users compared with non-users was not significantly higher (hazard ratio [HR] = 1.35, 95% CI = 0.85–2.13). However, zolpidem users with more than 180 cDDD in a year had an increased risk of developing AD than the users with less than 28 mg cDDD (HR = 4.18, 95% CI = 1.77–9.86) and non-zolpidem users (HR = 2.97, 95% CI = 1.61–5.49).

Results from the sensitivity analyses (Supplementary Table S1, Supplementary Table S2) showed the similarity of the results in the main analysis. In the first sensitivity analysis that evaluated the effect of the longer zolpidem exposure on the risk of AD, zolpidem users with more than 180 mg cDDD were found to have a higher hazard of developing AD when compared with users with less

Table 1. Baseline Characteristics of the Study Population Before and After Propensity Score Matching

	Before propensity score matching N = 11,318							After propensity score matching N = 6,922						
	Study population (n = 11,318)		Zolpidem use (n = 5,659)		Non-zolpidem use (n = 5,659)			Study population (n = 6,922)		Zolpidem use (n = 3,461)		Non-zolpidem use (n = 3,461)		
Characteristic	N	%	N	%	N	%	*P* value	N	%	N	%	N	%	*P* value
Age (mean, SD)	72.1	5.33	72.1	5.33	72.1	5.33	1.00	72.1	5.33	72.0	5.41	72.2	5.24	.34
Sex														
Female	7,028	62.1	3,514	62.1	3,514	62.1		4,351	62.9	2,116	61.1	2,235	64.6	
Male	4,290	37.9	2,145	37.9	2,145	37.9	1.00	2,571	37.1	1,345	38.9	1,226	35.4	1.00
Covariates														
Hypertension	6,036	53.3	3,557	62.9	2,479	43.8	<.01	3,970	57.4	2,006	58.0	1,964	56.7	.30
Stroke	1,466	13.0	995	17.6	471	8.3	<.01	851	12.3	424	12.3	427	12.3	.91
Myocardial infarction	146	1.3	109	1.9	37	0.7	<.01	73	1.1	36	1.0	37	1.1	.91
Hypercholesterolemia	2,252	19.9	1,390	24.6	862	15.2	<.01	1,424	20.6	712	20.6	712	20.6	1.00
Diabetes mellitus	2,246	19.8	1,366	24.1	880	15.6	<.01	1,450	20.9	736	21.3	714	20.6	.52
Depression	486	4.3	403	7.1	83	1.5	<.01	164	2.4	82	2.4	82	2.4	1.00
Anxiety	1,769	15.6	1,288	22.8	481	8.5	<.01	945	13.7	477	13.8	468	13.5	.75
Psychotic-related disorder	83	0.7	65	1.1	18	0.3	<.01	35	0.5	17	0.5	18	0.5	.87
Alcohol-related disoeder	32	0.3	24	0.4	8	0.1	<.01	18	0.3	12	0.3	6	0.2	.16
Sleep disorder	2,297	20.3	1,786	31.6	511	9.0	<.01	1,051	15.2	540	15.6	511	14.8	.33
Parkinson disease	156	1.4	113	2.0	43	0.8	<.01	76	1.1	38	1.1	38	1.1	1.00
Head Injury	264	2.3	169	3.0	95	1.7	<.01	163	2.4	80	2.3	83	2.4	.81
AntiHTN	7,106	62.8	4,155	73.4	2,951	52.1	<.01	4709	68.0	2,340	67.6	2,369	68.4	.45
AntiDM	1,786	15.8	1,081	19.1	705	12.5	<.01	1176	17.0	600	17.3	576	16.6	.44
Anticoagulant	2,819	24.9	1,786	31.6	1,033	18.3	<.01	1740	25.1	861	24.9	879	25.4	.62
Antilipidemia	1,624	14.3	992	17.5	632	11.2	<.01	1055	15.2	522	15.1	533	15.4	.71
Antidepressant	1,114	9.8	852	15.1	262	4.6	<.01	501	7.2	251	7.3	250	7.2	.96
BZD	6,221	55.0	4,121	72.8	2,100	37.1	<.01	4016	58.0	2,007	58.0	2,009	58.0	.96
AntiPD	412	3.6	274	4.8	138	2.4	<.01	194	2.8	82	2.4	112	3.2	.03*
Antipsychotics	1,402	12.4	930	16.4	472	8.3	<.01	772	11.2	380	11.0	392	11.3	.65
Outpatient visits due to mental disorder														
<6 times	1,478	13.1	1,004	17.7	474	8.4	<.01	857	12.4	423	12.2	434	12.5	.69
6–10 times	396	3.5	269	4.8	127	2.2	<.01	220	3.2	107	3.1	113	3.3	.68
11–15 times	260	2.3	188	3.3	72	1.3	<.01	126	1.8	61	1.8	65	1.9	.72
>15 times	96	0.8	70	1.2	26	0.5	<.01	47	0.7	21	0.6	26	0.8	.46

*$P < .05$.

Note: Baseline characteristics (age and sex) by cDDD exposure categories were listed in the Supplementary Table S3.

than 28 mg cDDD (HR = 3.27, 95% CI = 1.57–6.80) and non-zolpidem users (HR = 3.25, 95% CI = 1.70–6.20). In the second sensitivity analysis when including AD diagnosis given by all practitioners instead of the diagnosis only given by a psychiatrist or neurologist, zolpidem users with a high cumulative dosage were significantly associated with a higher risk of developing AD compared to non-users (HR = 1.93, 95% CI = 1.05–3.54). However, we did not find a difference in the risk of developing AD between zolpidem users and non-users (HR = 1.27, 95% CI = 0.84–1.93).

DISCUSSION

To our knowledge, this is the first observational study using a retrospective cohort study design to evaluate the association between the use of zolpidem and the risk of AD among older patients. Patients with a high cumulative dose of zolpidem had a significantly higher risk of developing AD when compared with patients with a low cumulative dose of zolpidem within 1 year.

Previous studies have found that the use of hypnotics was associated with an increased risk of dementia and AD.[16–19,21] Nonetheless, in those studies, the exposure of hypnotics was defined as a mixed use of benzodiazepine hypnotics and non-benzodiazepine hypnotics,[16,17,19,21,35] or benzodiazepine hypnotics only.[21] In contrast to the previous studies, our findings provide a new perspective in that we found zolpidem (a non-benzodiazepine hypnotic), taken by patients in higher doses (high cumulative dose), was associated with an increased risk of AD. Contrary to previous studies,[28,35] this study further assessed the effects of cumulative exposure of zolpidem on the risk of AD. This is an advantage because our study provided clinical evidence of an association between the cumulative dose effect of zolpidem use and the diagnosis of AD. Our study showed no increased risk of developing AD in zolpidem users when compared to non-users. However, we found

Table 2. Incidence of Alzheimer's Disease (AD) Between Zolpidem Users and Nonusers From 2006 to 2011 by Cumulative Defined Daily Doses (cDDD)[a] in One Year Since the Initiation

Study group	Number of AD				Follow-up (years)	
Exposures	n	%	n	%	Total	Mean
Non-zolpidem use	3,461	100.0	32	0.9	20,703	5.98
Zolpidem use	3,461	100.0	43	1.2	20,660	5.97
By zolpidem cumulative dosage in one year since the initiation						
Non-user	3,461	100.0	32	0.9	20,703	5.98
<28 cDDD	1,217	35.2	8	0.7	7,282	5.98
28–90 cDDD	1,240	35.8	15	1.2	7,414	5.98
91–180 cDDD	451	13.0	5	1.1	2,690	5.97
>180 cDDD	553	16.0	15	2.7	3,274	5.92

The cDDD was to add on the amount of zolpidem use per person in on year.

Note: Results from incidence of all types of dementia were listed in the Supplementary Table S4.

[a]DDD was defined as the average maintenance dose of zolpidem use per day for the major indication in one adult. The DDD of zolpidem was 10 mg.

Table 3. The Association Between Zolpidem Use and the Risk of Alzheimer's Disease (AD): Results of Cox Proportional Hazard Regression Models

Study group	Hazard ratio (95% CI)
Non-zolpidem use (n = 3,461)	Reference
Zolpidem use (n = 3,461)	1.35 (0.85–2.13)
By zolpidem cumulative dosage in one year since initiation	
Non-user	Reference
<28 cDDD	0.71 (0.32–1.54)
28–90 cDDD	1.31 (0.71–2.42)
91–180 cDDD	1.20 (0.47–3.09)
>180 cDDD	2.97 (1.61–5.49)
Zolpidem users	
<28 cDDDs	Reference
28–90 cDDDs	1.84 (0.78–4.34)
91–180 cDDDs	1.69 (0.55–5.17)
>180 cDDDs	4.18 (1.77–9.86)

Note 1: Results from the risk of all types of dementia were listed in the Supplementary Table S5.

Note 2: Results from a trend analysis of the association between the increased exposure of zolpidem use and risk of Alzheimer's disease were listed in the Supplementary Table S6.

Note 3: Results from the association between zolpidem use and risk of AD by sex (Supplementary Table S7) and age (Supplementary Table S8) showed the same results with the main analysis.

that high cumulative dose (>180 cDDD) within the first year after initiation was associated with a higher risk of developing AD, compared with low cumulative dose (<28 cDDD) or non-use of zolpidem. Our findings indicate that zolpidem was not associated with the risk of AD in older population but there is possibility of an increased risk of AD with high accumulative dose of zolpidem. Future studies are warranted to examine the risk of AD after long-term use or high dose of zolpidem.

Moreover, compared to previous studies using claims data,[19,28,35] our study had a relatively long follow-up period which enhances the ability to observe the occurrence of AD. With a long follow-up period and mainly focusing on the effect of non-benzodiazepine hypnotic use, our study provides a comprehensive investigation with results that inform health care providers of the need to be aware that higher cumulative doses of zolpidem are associated with an increased risk of dementia among older people within 1 year.

Our study is a retrospective cohort study with new user design[36,37] which mitigated biases and increased the study validity to better evaluate the association between the use of zolpidem and the increased risk of dementia when compared to previous studies conducted mainly using a nested case-control study design.[16,19,20,28] In addition, our study further confirmed that zolpidem users with higher cumulative doses had an increased risk of AD than lower dose users as well as non-zolpidem users. We ensured the temporal sequence between the exposure (zolpidem use) and the outcome (development of AD) was properly placed. For example, the one-year induction period we used was to minimize the bias of reverse causation.[36] Cases of AD, which occurred during the induction period, were not included as the outcome of this study.

Furthermore, we used propensity score to match the baseline characteristics between zolpidem users and non-zolpidem users. We found the overall health status of the non-zolpidem users was better than the users. The unbalance between exposure groups that is commonly observed in pharmacoepidemiological studies could cause confounding by indication bias and threaten the validity of the study.[32,33] The propensity score matching approach minimized the difference of characteristics and resulted in a more robust estimation.

Although the mechanism of the effect of zolpidem use on dementia remains unknown, a plausible pathway is through affecting calcium signaling of Cornu Ammonis 1 (CA1) hippocampal neurons. An animal study showed zolpidem may reduce the neuronal activity in the hippocampus, a crucial part of the brain for normal cognitive function and formation of new memories.[4] The effects of cumulative doses of zolpidem might cause continuing depressive effects on the hippocampus, and eventually reduce the cognitive function and cause memory loss. Furthermore, similar to benzodiazepines, zolpidem has a similar mechanism of action as benzodiazepines acting on the binding site of $GABA_A$ receptors.[13] With a similar pharmacologic implication, high cumulative doses of zolpidem could impair cognitive ability and lead to an increased risk for development of AD.

A high prevalence of zolpidem use was found in our study. About 15% of the older people in Taiwan were prescribed zolpidem during the study period. In addition, treatment with higher doses over long periods of time (high cumulative dose) was observed once treatment was started. For example, more than 15% of the new users had cumulative doses beyond 180 cDDD of zolpidem in 1 year. We also found a high prevalence of benzodiazepine use in both zolpidem user and non-zolpidem user groups. In Taiwan, the use of benzodiazepine is prevalent among older patients.[38] A high prevalent benzodiazepine use could further lower the cognitive function among older patients with AD because previous studies have reported a

positive association between the benzodiazepine use and the occurrence of AD.[16–19,21]

Inadequate management of sleep disorders among older patients in clinical practice is often unrecognized.[39] Unprecedented rates of adverse drug events could still occur among older zolpidem users due to the high prevalence and high cumulative dose of zolpidem use found in our study. It could also result in an overuse of zolpidem among these individuals. Due to the risk of zolpidem use among older patients, the most updated 2015 American Geriatrics Society (AGS) Beers Criteria for Potentially Inappropriate Medication Use in Older Adults has suggested that older patients should avoid any use of zolpidem when treating insomnia.[40] Therefore, a careful assessment of zolpidem use among older patients is necessary before zolpidem is initiated.[39]

Our study has several limitations. First, no clinical data such as clinical presentation, medical histories, neurological examinations, images, and biomarkers were available in our study.[41] These data are often used to diagnose AD. Only using ICD-9 CM codes to identify patients may not be valid enough. Misclassification and under-coding of AD remained possible.[42,43] Second, the database does not contain information on socioeconomic status, health lifestyle, and physical activities, which are also risk factors for AD.[44] The possible confounding effects of these immeasurable risk factors were unable to be eliminated in our study. Third, due to the length of available data, we only included patients with at least 6 years of follow-up time, which could possibly underestimate the risk of dementia. Fourth, although the propensity score matching mostly eliminated the unbalanced measured confounders between the zolpidem-user and non-user groups, the residual confounding by unmeasured variables such as the presence of unmeasured comorbidities, disease severity, and over the counter medication use could exist. Unbalanced comparison groups may still affect the risk estimation and lower the study validity. Fifth, we set a one-year induction period in the main analysis and two-year induction period in the sensitivity analysis to prevent the bias from reverse causation. However, due to the nature of the disease condition like dementia, which could have a gradual onset or be underdiagnosed for several years, the short induction period may still not completely eliminate the bias. Sixth, since all physicians can make an AD diagnosis in Taiwan, only patients with an AD diagnosis made by a psychiatrist or neurologist were counted so as to increase the outcome specificity. (Supplementary Table S9 described the number of psychiatrist/neurologist visits during the follow-up period between zolpidem user and nonuser groups.) However, this restriction could become a potentially important source of detection bias, as zolpidem users could be more likely to see these specialists and thus have a higher chance to receive an early diagnosis of AD. The restriction could also led to a population of patients with more severe AD, while undercounting those with milder onset of symptoms. Finally, patterns of zolpidem use identified from administrative claims data may overestimate the real consumption of zolpidem because a prescription refilled may not mean a prescription was taken. However, previous studies have shown the use of claims data was a relatively valid measurement of prescription use patterns.[45,46]

In conclusion, health care providers need to be mindful when prescribing zolpidem to older patients. A routine evaluation of older zolpidem users is necessary, especially for those with chronic insomnia. In order to lower the dependence with the medication, non-pharmacologic intervention such as the cognitive behavior therapy can be considered for older patients who use zolpidem.

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Conflict of Interest: Ms. Hui-Ting Cheng, Dr. Fang-Ju Lin, Dr. Steven R. Erickson, Dr. Jin-Liern Hong, and Dr. Chung-Hsuen Wu declare they have no conflict of interest related to the content or conduct of this study. This study was part of Ms. Cheng's masters thesis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Sensitivity Analysis with Two Years of Induction Period: Results of Cox Proportional Hazard Regression Models

Table S2. Incidence of Alzheimer's Disease (AD) between Zolpidem Users and Nonusers when Including AD Diagnosis Given by Any Practitioners

Table S3. Baseline Characteristics (Age and Sex) by Cumulative Defined Daily Doses cDDD Exposure Categories

Table S4. Incidence of Dementia among Zolpidem Users and Non-Zolpidem Users by Cumulative Defined Daily Doses (cDDD) in One Year Since Initiation

Table S5. Comparing Risk of Dementia among Zolpidem Exposure Groups After Propensity Score Matchings: Results of Cox Proportional Hazards Regression Model

Table S6. The Association between the Increased Exposure of Zolpidem Use and the Risk of Dementia: Results from a Trend Analysis

Table S7. The risk of Alzheimer's Disease between Zolpidem and Non-Zolpidem Users: Results of Cox Proportional Hazard Regression Model Stratified Analysis by Sex

Table S8. The Risk of Alzheimer's Disease between Zolpidem and Non-Zolpidem Users: Results of Cox Proportional Hazard Regression Model Stratified Analysis by Age

Table S9. Psychiatrist/neurologist Visits During the Follow-up Period by User Groups and Diagnosis with Alzheimer's Disease (AD)

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