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ORIGINAL ARTICLE

Benzodiazepines, z-Hypnotics, and Risk of Dementia: Special Considerations of Half-Lives and Concomitant Use

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Abstract

The utilization of benzodiazepines (BZDs) and z-hypnotics has substantially increased with the aging of the population, but the risk of BZDs and z-hypnotics in the development of dementia remains a strong concern. This cohort study aimed to evaluate the risk of BZDs and z-hypnotics for subsequent dementia development with a special consideration of their half-lives and the concomitant use of these medications. People aged 65 years and older who were newly prescribed oral BZDs or z-hypnotics between 2003 and 2012 were identified from Taiwan's National Health Insurance Research Database. All BZDs were categorized as long-acting drugs (≥ 20 h) or short-acting drugs (< 20 h) for further comparisons, and data were collected on a quarterly basis, starting on the first date of drug prescription and ending on the date of death, occurrence of dementia, or end of the follow-up period (December 31, 2012), whichever came first. All dementia events except vascular dementia occurring during the follow-up period were identified. Among 260,502 eligible subjects, short-acting BZDs and z-hypnotics users were at greater risk of dementia than long-acting users [adjusted odds ratio (95% confidence interval) in short-acting BZD users, 1.98 (1.89–2.07); z-hypnotic users, 1.79 (1.68–1.91); and long-acting BZD users, 1.47 (1.37–1.58)]. In addition, subjects concomitantly using 2 or more BZDs or z-hypnotics had a higher risk of dementia than those who used 1 of these drugs (4.79 (3.95–5.81)). The use of BZDs and z-hypnotics was strongly associated with the risk of dementia development, especially the short-acting BZDs, z-hypnotics, and concomitant use of multiple agents. These findings deserve further interventional studies for clarification.

Key Words Benzodiazepines · z-hypnotics · dementia · elderly · half-life

Introduction

Benzodiazepines (BZDs) and z-hypnotics (such as zolpidem) are widely prescribed to older adults for various purposes, either alone or in combination with other disease-related treatments [1–4]. Despite the risk of BZD- or z-hypnotic-related falls, fractures, traffic accidents, and cognitive dysfunction [5–7], considerable research and public attention have focused on the association between BZDs or z-hypnotics and the risk of dementia [5, 8–14]. However, this association remains less well understood, and symptoms that BZDs or z-hypnotics are indicated for may be the prodromal symptoms of dementia. The use of BZDs and z-hypnotics may result in acute cognitive decline [15], but evidence regarding their long-term use and cognitive decline varies greatly [16–21]. Although some studies have suggested that BZDs and z-hypnotics may not have long-term effects [16, 17], others have reported a potential association between the use of BZDs and z-hypnotics and the subsequent development of dementia or Alzheimer's disease [22, 23].

Li-Yen Tseng and Shih-Tsung Huang contributed equally to this work.

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These discrepancies in previous studies may have resulted from different methodological limitations. First, available reports often group all BZDs together without consideration of their pharmacological properties, such as their half-lives, i.e., short- or long-acting BZDs [11, 12]. Second, many existing studies have often investigated the association between individual BZDs or z-hypnotics and the risk of dementia [8–12]. However, older adults often switch their medications between the 2 classes of drugs, as well as between short- and long-acting BZDs. These utilization patterns made it difficult to capture the *actual* effects of long-term use of BZDs and/or z-hypnotics and risk of dementia. Novel techniques to capture the *real-world* utilization patterns of BZDs or z-hypnotics are, thus, critical to fill the knowledge gap regarding the associations between BZDs or z-hypnotics and risk of dementia.

To overcome these limitations of previous studies, we conducted a longitudinal cohort study to investigate the association between BZDs or z-hypnotics and the risk of dementia by adopting time-varying (quarterly) measures of exposure to BZDs or z-hypnotics. Furthermore, we also aimed to test the hypothesis that BZDs with different half-lives may have a differential impact on dementia risk.

Methods

Data Source

A population-based retrospective longitudinal cohort study was conducted using administrative health data from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD is a nationwide claims-based database comprising anonymous eligibility and enrollment information, as well as claims for outpatient visits, admissions, procedures, and prescription medications of more than 99% of the entire population (23 million) in Taiwan [24]. We used a subset of the NHIRD, which contains claims data for 20% of randomly selected beneficiaries who were aged 65 years old and older from 2004 to 2008 to create a 10-year (2003–2012) panel of claims for analysis.

Ethical Statement

The identification numbers for all of the entries in the NHIRD were encrypted to protect the privacy of the individual patients. The study protocol was approved by the Institution Review Board of the National Taiwan University Hospital (National Taiwan University Hospital Research Ethics Committee No. 201403069W).

Study Population

From the NHIRD, we identified elderly individuals aged 65 years and older who initiated the use of oral BZDs or z-hypnotics in an outpatient setting between 2003 and 2012 as our study cohort. The index date was defined as the date of first prescription of oral BZDs or z-hypnotics. The last year before the index date served as the baseline information-taking period. The follow-up period for each study subject started on the index date and ended on the date of death, the date of a dementia event, or December 31, 2012, whichever came first. Those who had ever received oral BZDs or z-hypnotics and were diagnosed with dementia in the outpatient or inpatient setting within 1 year prior to the index date were excluded. To prevent lag time bias, we also excluded patients who had any diagnosis of dementia in the outpatient or inpatient setting in the first year of the follow-up period. In addition, to explore the risk of drug-related dementia events, we excluded individuals who had vascular dementia (with an International Classification of Disease, 9th Edition, diagnosis code (ICD-9-CM codes) 290.4) or those who were diagnosed with dementia within 1 year after stroke occurring during the follow-up period.

Drug Exposure

We assumed that the use of BZDs and z-hypnotics was a dynamic process since older persons may discontinue, switch, or reinitiate the use of these drugs very frequently; therefore, we measured BZD and z-hypnotic use quarterly to identify the actual utilization of BZDs and z-hypnotics during the follow-up period. In addition, as we intended to test the hypothesis that half-lives of BZDs were associated with different risk levels of dementia, we distinguished between the use of long-acting BZDs (half-life $\geq$20 h) and short-acting BZDs (half-life $<$20 h) according to their half-lives [25, 26] (Table 1), and this cutoff time was based on previous studies [9, 10].

Exposure to BZDs and z-hypnotics was defined as receiving at least 28 days of the same half-life class of BZDs or z-hypnotics in a quarter and recorded as a time-varying binary variable. Moreover, considering that some subjects may use more than 2 classes of BZDs or z-hypnotics in the same quarter, we further categorized the utilization pattern of BZDs and z-hypnotics as 1) nonuse, 2) only long-acting BZDs, 3) only short-acting BZDs, 4) only z-hypnotics, 5) long-acting BZDs + short-acting BZDs (2 combined), 6) long-acting BZDs + z-hypnotics (2 combined), 7) short-acting BZDs + z-hypnotics (2 combined), and 8) long-acting BZDs + short-acting BZDs + z-hypnotics (3 combined). For sensitivity analysis, we changed the definition of drug exposure as the use of the same drug class for at least 1 day, 7 days, or 14 days in each quarter.

Table 1 Half-life and Anatomical Therapeutic Chemical (ATC) code for benzodiazepine and z-drug

Type	Drug name (half-life, in h)	ATC code
Long-acting (half-life ≥ 20 h)	Bromazepam (20.6)	N05BA08
	Chlordiazepoxide (24–48)	N05BA02
	Clobazam (36–42)	N05BA09
	Clonazepam (30–40)	N03AE01
	Diazepam (48)	N05BA01
	Nitrazepam (24–29)	N05CD02
	Prazepam (78)	N05BA11
	Medazepam (36–200)	N05BA03
	Nordazepam (36–200)	N05BA16
	Flunitrazepam (18–26 but 36–200 for active metabolite)	N05CD03
	Oxazolam (61.2)	N05BA91
	Brotizolam (4–8)	N05CD09
Short-acting (half-life < 20 h)	Alprazolam (10.7–15.8)	N05BA12
	Clorazepate (2.3)	N05BA05
	Estazolam (10–24)	N05CD04
	Flurazepam (2.3)	N05CD01
	Lorazepam (12–14)	N05BA06
	Midazolam (1.8–6.4)	N05CD08
	Oxazepam (5.6–10.9)	N05BA04
	Temazepam (3.5–18.4)	N05CD07
	Triazolam (1.5–5.5)	N05CD05
	Lormetazepam (10–12)	N05CD06
z-drug	Zolpidem (2.5–2.6)	N05CF02
	Zaleplon (1)	N05CF03
	Zopiclone (3.5–6.5)	N05CF01
	Eszopiclone (6–9)	N05CF04

Outcome Measurement

The outcome of interest was dementia and defined as a diagnosis documented with 1 of following ICD-9-CM codes: 290.xx (dementias), 294.1 (dementia in conditions classified elsewhere), 331.0 (Alzheimer disease), and 331.2 (Senile degeneration of brain), with the exception of 290.4 (vascular dementia). We considered the dementia diagnosis to be valid if it was documented at least 3 times in outpatient visits or 1 inpatient hospitalization. The study design is shown in Figure S1.

Other Variables

The age and sex of subjects were documented at the index date. We also retrieved each subject's medical history within 1 year prior to the index date for an estimation of Charlson Comorbidity Index (CCI) [27] as a proxy of a subject's health status and other comorbidities, including hypertension, insomnia, cerebrovascular disease, dyslipidemia, myocardial infarction, diabetes, depression, psychosis, schizophrenia, delirium, bipolar disorder, and anxiety. In addition, because a previous study indicated that using drugs with anticholinergic effects [28] may be associated with dementia, we also recorded the anticholinergic cognitive burden (ACB) score during the follow-up period as a time-varying (quarterly) covariate. These variables were included in this analysis model.

Statistical Analysis

Chi-square tests and ANOVAs were used to compare categorical and continuous variables, respectively. Generalized estimating equation (GEE) models (SAS PROC GENMOD) with logit link and first-order autoregressive (AR-1) correlation structure were used to examine the association between distinct half-lives of BZDs and the risk of dementia, taking into account the intraclass correlation between repeated measurements for the same subjects. The GEE models were further adjusted for age, sex, CCI, comorbidity, and time-varying covariates, including the number of quarters since the index date and ACB score. These associations were presented as odds ratios (ORs) with 95% confidence intervals (CIs). All of the analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

We identified 417,581 subjects who were 65 years or older and initiated BZDs or z-hypnotics between 2003 and 2012. Approximately 70% (n = 287,020) of these subjects were new users of BZDs or z-hypnotics. We excluded those who had dementia within 1 year before the index date or 1 year after the index date (n = 20,743) and those who were diagnosed with vascular dementia or had dementia within 1 year after stoke during follow-up period (n = 5775). Overall, we included data from 260,502 older adults who newly initiated the use of BZDs or z-hypnotics in our analysis (Fig. 1).

As summarized in Table 2, we categorized study subjects into long-acting BZD users (n = 127,682; 49%), short-acting BZD users (n = 96,657; 37%), and z-hypnotic users (n = 127,682; 14%) according to their first prescription of a BZD or z-hypnotic at the index date. Demographic characteristics at the index date differed significantly across the 3 groups. Overall, short-acting BZD and z-hypnotic users at the index date had higher CCI and were more likely to have other comorbidities than long-acting BZD users. After adjustment for age, sex, CCI, depression, psychosis, delirium, bipolar, anxiety, and ACB scores, GEE models (Table 3) indicated that short-acting BZD and z-hypnotic users had a higher risk of dementia than long-acting BZD users (short-acting BZD users: adjusted odds ratio (aOR) = 1.98, 95% CI = 1.89–

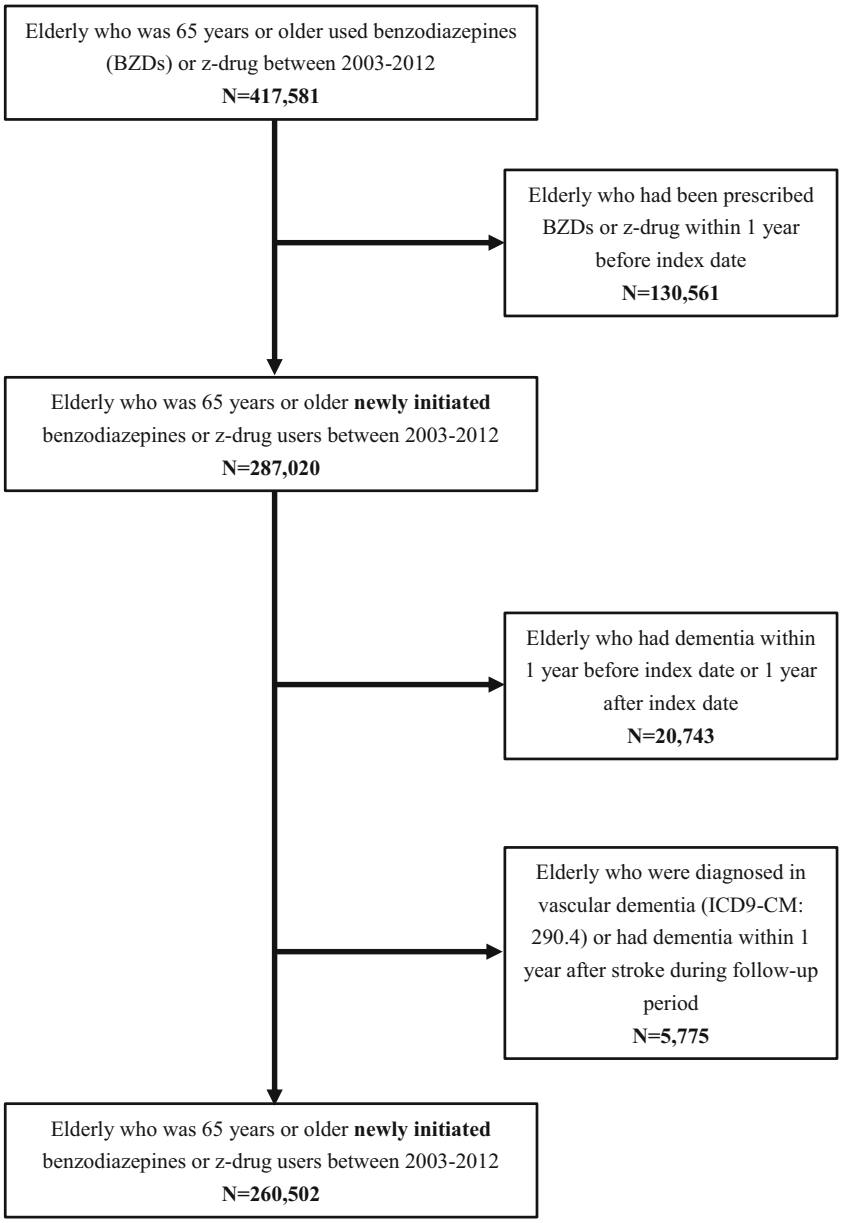

Fig. 1 Study flow chart of inclusion and exclusion of study objects

2.07; z-hypnotic users: aOR = 1.79, 95% CI = 1.68–1.91; long-acting BZD users: aOR = 1.47, 95% CI = 1.37–1.58). In addition, long-acting BZDs, short-acting BZDs, and z-hypnotics were all associated with a higher risk of dementia than nonusers. GEE models also revealed that the subjects using 2 or more classes of BZDs or z-hypnotics in the same quarter had a higher risk of dementia (long-acting + short-acting BZD users: aOR = 2.96, 95% CI = 2.64–3.36; long-acting BZD + z-hypnotic users: aOR = 2.82, 95% CI = 2.42–3.28; short-acting BZD + z-hypnotic users: aOR = 3.25, 95% CI = 2.97–3.56) than the subjects who only used any 1 class of the drugs; this higher risk was especially true for subjects who concomitantly used long-acting BZDs, short-acting BZDs, and z-hypnotics in the same quarter (aOR = 4.79, 95% CI = 3.95–5.81).

In the sensitivity analysis, we changed the definition of drug exposure from using 28 days or more to using 1 day, 7 days, or 14 days or more as cut-points in each quarter. We found that all 3 models yielded results similar to our primary findings (Table 4).

Interpretation

This population-based retrospective cohort study evaluated the potential associations between long-term and dynamic

Table 2 Baseline characteristics of study subjects who newly initiated long-acting, short-acting, and z-drug, a subgroup by the kind of prescription in the index date

	Long-acting BZD (n = 127,682)		Short-acting BZD (n = 96,657)		z-drug (n = 36,217)		Total (n = 260,502)
	n	%	n	%	n	%	p value
Age (years)							
Mean ± SD	72.76 ± 6.21		73.36 ± 6.68		73.24 ± 6.83		< 0.001
65–75	82,746	64.83	59,127	61.17	22,308	61.60	
75–85	38,720	30.34	30,799	31.86	11,270	31.12	
85+	6162	4.83	6731	6.96	2639	7.29	
Sex							
Female	65,102	51.01	50,526	52.27	18,252	50.40	< 0.001
Male	62,526	48.99	46,131	47.73	17,965	49.60	
CCI							
Mean ± SD	0.79 ± 1.19		1.10 ± 1.53		1.22 ± 1.60		< 0.001
0–2	117,256	91.87	83,839	86.74	30,618	84.54	
2+	10,372	8.13	12,818	13.26	5599	15.46	
Comorbidity							
Depression	887	0.69	1082	1.12	438	1.21	< 0.001
Psychosis	188	0.15	391	0.40	165	0.46	< 0.001
Schizophrenia	103	0.08	255	0.26	108	0.30	< 0.001
Delirium	32	0.03	47	0.05	28	0.08	< 0.001
Bipolar	81	0.06	89	0.09	39	0.11	0.008
Anxiety	3488	2.73	3694	3.82	1310	3.62	< 0.001
Hypertension	51,603	40.43	44,554	46.09	17,657	48.75	< 0.001
Insomnia	3493	2.74	4529	4.69	2554	7.05	< 0.001
Hyperlipidemia	14,361	11.25	12,279	12.70	5054	13.95	< 0.001
Myocardial infarction	842	0.66	1311	1.36	445	1.23	< 0.001
Diabetes	21,724	17.02	18,933	19.59	8094	22.35	< 0.001
Stroke	9880	7.74	9602	9.93	4071	11.24	< 0.001

use of BZDs and z-hypnotics and the risk of dementia among individuals aged 65 years and older with a more sophisticated study design than previous studies. The major strength of our study was to capture the long-term and dynamic use of these drugs and thus was able to bridge the knowledge gap involving the *switch* between different classes of hypnotics that has rarely been done in previous studies. Furthermore, we found that both short-acting and long-acting BZDs led to a greater risk of dementia. To the best of our knowledge, this is the first study considering all these factors to clarify the risk of BZDs and z-hypnotics on dementia. Compared to the nonusers, older people using BZDs (either long-acting or short-acting ones) or z-hypnotics for more than 28 days during every quarter of the year had a greater risk of dementia (47% greater for long-acting BZDs, 98% for short-acting BZDs, and 79% for z-hypnotics). We also found that the elderly population that used more than 1 class of sedatives (either BZDs or z-hypnotics) had a higher risk of dementia than the population that used a single drug class. The risk of dementia was 4.79-fold higher in long-acting BZD + short-acting BZD + z-hypnotic (3 combined) users than nonusers. Those with the combined use of short-acting BZDs and z-hypnotics had a 3.25-fold higher risk of dementia than the nonusers.

Our study showed that short-acting BZDs and z-hypnotics users had a higher risk of dementia than long-acting BZDs users. Previous studies have shown that long-acting BZDs (half-life > 20 h) are at higher risk than short-acting ones in the risk of dementia development [8–10]. Takada et al. [8] conducted a study and established the associations between BZD use and dementia from 3 large databases and reported that long-acting BZD use was strongly associated with an increased risk of dementia than short-acting BZD use. A case–control study in Quebec enrolled 1796 people with incident Alzheimer's disease matched with 7184 controls and found that ever use of BZDs was associated with a 51% higher risk of Alzheimer's disease [9]. The association between Alzheimer's disease and BZD use was stronger for long-acting BZDs (HR = 1.70, 95% CI = 1.46 to 1.98) than short-acting ones (HR = 1.43, 95% CI = 1.27 to 1.61). The Three-City Study from France also reported a substantial risk of

Table 3 Association between distinct half-life of BZD and z-drug and the risk of dementia adjusted for quarter, age, sex, CCI, ACB, and comorbidities

	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
BZD				
Nonuser	ref		ref	
Long-acting BZD (L)	1.48	1.37–1.59	1.47	1.37–1.58
Short-acting BZD (S)	2.31	2.21–2.41	1.98	1.89–2.07
z-drug (Z)	1.92	1.81–2.05	1.79	1.68–1.91
L + S	3.18	2.83–3.58	2.96	2.64–3.36
L + Z	2.88	2.48–3.35	2.82	2.42–3.28
S + Z	3.77	3.46–4.10	3.25	2.97–3.56
L + S + Z	5.04	4.18–6.09	4.79	3.95–5.81
Others				
Quarter			1.05	1.05–1.05
Age (years)				
65–75			ref	
75–85			2.59	2.51–2.68
85+			5.32	5.02–5.63
Sex				
Female			ref	
Male			0.92	0.89–0.95
CCI				
0–2			ref	
2+			1.44	1.42–1.46
ACB score			1.34	1.27–1.41
Comorbidity				
Depression			1.05	0.90–1.22
Psychosis			1.74	1.39–2.18
Delirium			3.37	2.00–5.68
Bipolar			1.97	1.37–2.82
Anxiety			0.89	0.81–0.97

CCI = Charlson Comorbidity Index; ACB = anticholinergic cognitive burden

long-acting BZDs in dementia development (HR = 1.62, 95% CI = 1.11 to 2.37) through a prospective study design, and the risk of short-acting BZDs was only marginal (HR = 1.05, 95% CI = 0.85 to 1.3) [10]. One potential explanation for the abovementioned discrepancies could be that short-acting BZD users and z-hypnotic users in our study were older and had more multimorbidity than the long-acting BZD users. Moreover, long-acting BZDs have been considered potentially inappropriate medications for older adults [29, 30], and therefore, the utilization may have been reduced in older populations. This phenomenon could imply that physicians may prefer short-acting BZDs or z-hypnotics for older people because of their older age and multiple comorbid conditions, as well as the strong risk of falls associated with long-acting BZDs.

A number of studies have shown the adverse cognitive and memory effects of BZDs and z-hypnotics [31–34], including both nonamnestic and amnestic cognitive impairment. Both BZDs and z-hypnotics are gamma-aminobutyric acid (GABA)-ergic agents and function as positive allosteric modulators of GABA-A receptors [6, 35–39]. After GABA-A receptors are bound by BZDs or z-hypnotics, the chloride ion channel is opened, resulting in central nervous system (CNS) inhibition and subsequent adverse effects. Previous studies indicated that BZD use might decrease the expression of GABA-A receptors in synapses, which could decrease postsynaptic inhibition [40, 41]. In addition, BZD use would also affect GABA-A receptor–mediated synaptic currents in the hippocampal cornu ammonis area 1 (CA1) pyramidal neurons, which may affect the balance of excitation and inhibition in the CNS [41, 42]. In addition to the synaptic effects of BZDs and z-hypnotics, both BZDs and z-hypnotics may bind to BZD-1 receptors, 1 of the subtypes of BZD receptors in the CNS that has been associated with sedative effects and anterograde amnesia [36].

Although many studies have shown associations between BZDs and z-hypnotics and dementia, the exact mechanisms remain unclear. A previous study suggested that the BZD-induced inhibitory GABA effect in the CNS may reduce the activity of beta secretase and gamma secretase, which are protective against cognitive declines [43]. However, new therapeutic agents inhibiting gamma secretase have not shown significant effects on dementia compared to placebo [44, 45]. Moreover, some unfavorable effects of the gamma secretase inhibitor semagacestat (LY-450139) have been reported. Another hypothesis is that "excitotoxicity" may occur in the overactivated CNS [46]. The potential *calm-down* effects of BZDs in the CNS may play some role in dementia protection, but it is difficult to evaluate the excitation toxicity of each individual drug. Although the protective effects of BZDs against cognitive impairment had been proposed based on findings in the laboratory, the real-world data was showing the opposite effects in that BZD use was associated with a higher risk of dementia. Further study evaluating the pharmacological effects of BZDs and z-hypnotics on cognitive function is needed to confirm the roles of these pharmacological agents in cognitive health.

The strength of this study included the large study sample size and the dynamic relationship between BZD and z-hypnotic use, as well as the special consideration of the half-lives of individual drugs and their concomitant use. The study design enabled us to explore the complex interrelationship between real-world patterns of BZD and z-hypnotic use and the risk of dementia. However, some limitations still exist despite all the effort that went into the study. First, some factors related to cognitive function, such as education, smoking, alcohol consumption, family history, Apo-E4, and baseline cognitive function, were not available in the dataset.

Table 4 Association between distinct half-life of BZD and z-drug and the risk of dementia with 1 day, 7 days, and 14 days cut-point of drug exposure

Cut-point	1 day		7 days		14 days	
	OR	95% CI	OR	95% CI	OR	95% CI
BZD						
Nonuser	ref		ref		ref	
Long-term BZD (L)	1.17	1.10–1.24	1.42	1.33–1.52	1.51	1.41–1.62
Short-term BZD (S)	2.03	1.94–2.12	2.15	2.06–2.25	2.15	2.05–2.24
z-drug (Z)	1.9	1.78–2.02	1.92	1.80–2.04	1.93	1.81–2.05
L + S	2.96	2.74–3.20	3.64	3.34–3.97	3.51	3.19–3.88
L + Z	2.62	2.33–2.95	3.01	2.65–3.42	2.94	2.56–3.38
S + Z	4.05	3.79–4.34	4.23	3.94–4.53	3.94	3.65–4.25
L + S + Z	6.07	5.52–6.67	6.67	5.95–7.46	6.22	5.43–7.13
Others						
Quarter	1.05	1.05–1.05	1.05	1.05–1.05	1.05	1.05–1.05
Age (years)						
65–75	ref		ref		ref	
75–85	2.64	2.55–2.73	2.63	2.54–2.72	2.61	2.53–2.70
85+	5.45	5.15–5.77	5.43	5.13–5.74	5.38	5.09–5.70
Sex						
Female	ref		ref		ref	
Male	0.93	0.90–0.96	0.93	0.90–0.96	0.92	0.89–0.95
CCI						
0–2	ref		ref		ref	
2+	1.34	1.27–1.42	1.33	1.26–1.40	1.33	1.26–1.40
ACB score	1.40	1.38–1.42	1.40	1.38–1.43	1.42	1.40–1.44
Comorbidity						
Depression	1.04	0.90–1.21	1.00	0.86–1.16	1.01	0.87–1.17
Psychosis	1.81	1.45–2.28	1.74	1.39–2.19	1.72	1.37–2.16
Delirium	3.30	1.94–5.64	3.25	1.91–5.53	3.28	1.94–5.55
Bipolar	1.97	1.37–2.83	1.91	1.33–2.75	1.92	1.34–2.76
Anxiety	0.87	0.79–0.94	0.85	0.78–0.93	0.86	0.78–0.93

CCI = Charlson Comorbidity Index; ACB = anticholinergic cognitive burden

However, this is the common situation with claims data that is universal across other studies. Second, we excluded vascular dementia in this study due to the small reported case number and the lack of brain images to confirm the diagnosis. However, other types of dementia with specific etiologies may have been included in the diagnostic entity of dementia because most physicians may not clearly differentiate those patients in their daily practice. However, the case number of other types of dementia was small, so the results of the study may remain similar with or without specific classification of the etiology. Third, similar to all claims data-based studies, adherence to the medications for the study subjects was unknown, which may result in overestimating the adverse effects of BZDs and z-hypnotics. Fourth, a 10-year (2003–2012) panel of claims for the analysis may not be long enough to confirm the risk of dementia following the use of these pharmaceutical agents. Fifth, the algorithm we adopted to identify dementia via discharge diagnosis at inpatient visits may not have guaranteed that these cases had subsequent dementia diagnoses at outpatient visits. We thus conducted sensitivity analyses by excluding those discharged with a dementia diagnosis but without a dementia diagnosis in subsequent outpatient visits (n = 1326) (Table S1). The results were consistent between the original model (dementia cases, n = 23,919) and sensitivity analyses (dementia cases, n = 22,593). Therefore, we believe our findings are robust.

Conclusions

In conclusion, the results of this study suggested that the use of BZDs and/or z-hypnotics may increase the risk of dementia

in a 10-year follow-up period, and the concomitant use of these agents significantly increases the risk. Moreover, short-acting BZDs and z-hypnotics were of greater risk of dementia than long-acting BZDs. Further intervention studies are needed to confirm the causal relationships between the use of BZDs and z-hypnotics and the risk of dementia.

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Author Contributions All the authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published. LY Tseng, ST Huang, and FY Hsiao designed the research and wrote the paper. LY Tseng performed the literature search. ST Huang performed the data analysis. FY Hsiao provided critical methodological and statistical inputs. LY Tseng, LN Peng, and LK Chen contributed to the clinical interpretation. FY Hsiao is the guarantor.

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