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Association Between Benzodiazepine Use and Epilepsy Occurrence

A Nationwide Population-Based Case–Control Study

Tomor Harnod, MD, PhD, Yu-Chiao Wang, MSc, and Chia-Hung Kao, MD

Abstract: We conducted a retrospective case–control study to evaluate the association between the risk of benzodiazepine (BZD) use and epilepsy occurrence by using data from the Taiwan National Health Insurance Research Database.

We recruited 1065 participants who ages 20 years or older and newly diagnosed with epilepsy (International Classification of Diseases, Ninth Revision, Clinical Modification 345) between 2004 and 2011 and assigned them to the epilepsy group. We subsequently frequency-matched them with participants in a control group (n = 4260) according to sex, age, and index year at a 1:4 ratio. A logistic regression model was employed to calculate the odds ratio (OR) for association of epilepsy with BZD exposure. Multivariate logistic regression was conducted to estimate the dose–response relationship between BZD levels and epilepsy risk.

The adjusted OR (aOR) for the association of epilepsy with BZD exposure was 2.02 (95% confidence interval [CI] = 1.68–2.42). The aOR for an average BZD dose increased to 1.26 for the participants on <0.01 defined daily dose (DDD), and increased to 4.32 for those on ≥1.50 DDD. On average, when the DDD of BZD exposure increased by 100 units, the epilepsy risk increase by 1.03-fold (95% CI = 1.01–1.04, $P = 0.003$). The annual BZD exposure day ranges were significantly associated with epilepsy (2–7 days: aOR = 1.67; 8–35 days: aOR = 3.16; and ≥35 days: aOR = 5.60). Whenever the annual BZD exposure increased by 30 days, the risk of epilepsy notably increased by 1.03-fold (95% CI = 1.01–1.04, $P < 0.001$). In addition, users who quit BZD for more than 6 months still exhibited a higher risk of epilepsy than did the non-BZD users.

A considerable increase in epilepsy occurrence was observed in ones with BZD use, particularly in those with prolonged use, multiple exposure, and high-dose consumption.

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Abbreviations: aOR = adjusted odds ratio, ATC = Anatomical Therapeutic Chemical, BZDs = benzodiazepines, CI = confidence interval, CNS = central nervous system, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes.

INTRODUCTION

Benzodiazepines (BZDs) are a class of psychoactive drugs used worldwide for treating or controlling various neurological and psychiatric conditions, such as epileptic seizures, agitation, anxiety, and sleep disorders. BZDs enhance GABAergic transmission and have been widely used clinically for numerous years. Several recent studies in the United States and Taiwan have indicated that sleeping pills (most of which are BZDs) can increase the risk of various types of neoplasm, such as brain tumors, and shorten the life span of users.[1–3] In addition, studies have reported that BZD might be associated with a secondary hyperexcitability phenomenon in an interdose time because of the withdrawal or rebound effect and result in substantial activation of neuronal hyperexcitability.[4,5] Although extensive literature is available on using BZD for modulating the central nervous system (CNS) and controlling seizure,[6] additional data are required to clarify the potential risk of epileptogenesis in the CNS and epilepsy in BZD users.

To determine whether long-term or excessive BZD use can be an independent risk factor for epilepsy in adulthood, we retrospectively analyzed data from a Taiwanese nationwide population-based database and evaluated the relationship between the epilepsy risk and BZD use.

METHODS

Database

We conducted a case–control study by using data from Taiwan's National Health Insurance Research Database

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From the Department of Neurosurgery, Hualien Tzu Chi General Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan (TH); College of Medicine, Tzu Chi University, Hualien, Taiwan (TH); Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan (Y-CW); College of Medicine, China Medical University, Taichung, Taiwan (Y-CW); Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan (C-HK); and Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan (C-HK).
Correspondence: Chia-Hung Kao, Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan (e-mail: d10040@mail.cmuh.org.tw).
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(NHIRD). The NHIRD was established in 1996 and contains reimbursement claims data from the single-payer National Health Insurance program, which was launched in 1995 and covered approximately 99% of the residents of Taiwan by the end of 2007. The annual claims data in the NHIRD are managed by the National Health Research Institutes. The Longitudinal Health Insurance Database (LHID) is a subset of the NHIRD and is used for medical research. The LHID comprises 1 million randomly sampled insured representatives of the entire population in Taiwan. The database maintains standard claims data, such as demographic data, medications, treatments, and disease diagnoses, of the enrollees availing healthcare facilities because of health problems. Specific patient illnesses were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. All data were deidentified and analyzed anonymously under the personal data protection law. The Ethics Review Board of China Medical University approved this study (CMUH104-REC2-115).

Study Participants

Figure 1 shows a flowchart of the selection process adopted in our study. We recruited participants who ages 20 years or older from the NHIRD (n = 872,883). Among these participants, 8904 were diagnosed with epilepsy (ICD-9-CM 345) between 1996 and 2011. Participants with brain tumors (ICD-9-CM 225, 191, 192, 194.3, and 194.4), head injury (ICD-9-CM 850–854 and 959.01), or stroke (ICD-9-CM 430–438) were excluded (n = 2770). Therefore, 1065 participants with newly diagnosed epilepsy between January 1, 2004 and December 31, 2011 were finally enrolled into the epilepsy group. The date of epilepsy diagnosis was defined as the index date. The control group (n = 4260) comprised randomly selected participants without epilepsy, who were frequency matched with participants in the epilepsy group according to age (per 5 years), sex, and index year.

The history of BZD use since 1996 was calculated for each participant and presented according to the average defined daily dose (DDD) of BZD by the Anatomical Therapeutic Chemical (ATC) classification system (eg, diazepam 10 mg/day is equal to 1 DDD of BZD),[7] from the first BZD exposure date to the index date. Diazepam (ATC code: N05BA01), chlordiazepoxide

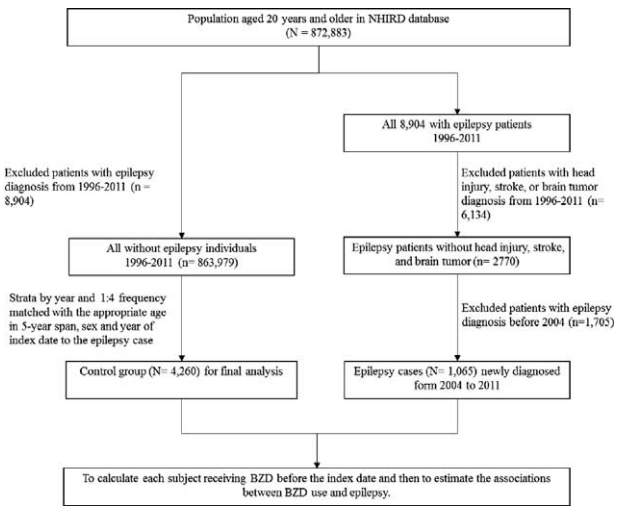

FIGURE 1. The flowchart presents selection of the study participants. NHIRD = National Health Insurance Research Database.

(ATC code: N05BA02), medazepam (ATC code: N05BA03), oxazepam (ATC code: N05BA04), potassium clorazepate (ATC code: N05BA05), lorazepam (ATC code: N05BA06), bromazepam (ATC code: N05BA08), clobazam (ATC code: N05BA09), prazepam (ATC code: N05BA11), alprazolam (ATC code: N05BA12), nordazepam (ATC code: N05BA16), fludiazepam (ATC code: N05BA17), cloxazolam (ATC code: N05BA22), flurazepam (ATC code: N05CD01), nitrazepam (ATC code: N05CD02), flunitrazepam (ATC code: N05CD03), estazolam (ATC code: N05CD04), triazolam (ATC code: N05CD05), lormetazepam (ATC code: N05CD06), midazolam (ATC code: N05CD08), brotizolam (ATC code: N05CD09) were the BZD categories. We calculated the average BZD exposure day, which was derived by dividing the total BZD exposure days by the total follow-up time (from the first BZD exposure date to the index date). We classified the average BZD dose by using 2 approaches: stratifying the BZD exposure into yes or no and categorizing the DDD (none, <0.01, 0.01–0.09, 0.09–1.50, and ≥1.50 per day) according to a quartile method. In addition, the quartile method was adopted to classify the annual BZD exposure days (none, <2, 2–7, 8–35, or ≥35 days).

In addition to the demographic risk factors (age and sex), we evaluated other potential confounding factors for epilepsy, such as dementia (ICD-9-CM 290.0–290.4 and 331.0), anxiety (ICD-9-CM 300.0, 300.2, 300.3, 308.3, and 309.81), depression (ICD-9-CM 296.2–296.3, 300.4, and 311), and sleep disorders (ICD-9-CM 307.4 and 780.5), except for sleep apnea syndrome (ICD-9-CM 780.51, 780.53, and 780.57).

Statistical Analyses

Participant distribution was analyzed according to demographic characteristics. To evaluate demographic differences between the non-BZD and BZD users, the Chi-squared test was used for categorical variables, and Student *t* test was used for continuous variables. We used both statistical methods to evaluate the difference between the epilepsy and control groups. To estimate the associations between BZD use and epilepsy, we used logistic regression and presented the crude odds ratio (OR) and 95% confidence intervals (CIs). The adjusted OR (aOR) was determined using multivariate logistic regression after adjustment for sex, age, dementia, anxiety, depression, and sleep disorders. The BZD dose–response and annual BZD exposure day were measured, and the relationship between the diverse BZD exposure levels and the risk of epilepsy was further analyzed using multivariate logistic regression. Furthermore, we evaluated the association between BZD and epilepsy according to various durations of BZD use (1 week, 1 month, 3 months, 6 months, and 1 year). The final analysis revealed the association between various BZD quitting days and epilepsy (<7, 8–30, 31–90, 91–180, and ≥180 days).

All data management and statistical analyses were conducted using the SAS 9.4 package (SAS Institute Inc., Cary, NC). All statistical tests were 2-sided, and a 2-tailed *P* value of <0.05 was considered significant.

RESULTS

Table 1 lists the demographic characteristics and comorbidities of all 5325 participants classified as non-BZD (n = 1706) and BZD users (n = 3619). Regardless of sex, the percentage of BZD users was higher than that of non-BZD users (Chi-squared test, $P < 0.001$). The BZD users were older than the non-BZD users (52.1 vs 41.0 years, Student *t* test,

TABLE 1. Demographics Characteristics Between Non-BZD Users and BZD Users

	Non-BZD Users, N = 1706			BZD Users, N = 3619			
Variables	**N**	**Case**	**%**	**N**	**Case**	**%**	***P* Value**
Sex							
Women	621	70	11.3	1779	410	23.1	<0.0001
Men	1085	127	11.7	1840	458	24.9	<0.0001
Age at index date, yr							
Age, mean (SD), yr*		41.0 (15.6)			52.1 (18.2)		<0.0001
20–34	714	87	12.2	771	210	27.2	<0.0001
35–44	416	47	11.3	654	167	25.5	<0.0001
45–54	265	32	12.1	670	155	23.1	0.0001
55–64	170	14	8.24	550	130	23.6	<0.0001
≥65	141	17	12.1	974	206	21.2	0.0116
Comorbidity							
Sleep disorders							
No	1602	181	11.3	2393	501	20.9	<0.0001
Yes	104	16	15.4	1226	367	29.9	0.0017
Dementia							
No	1702	196	11.5	3519	828	23.5	<0.0001
Yes	4	1	25.0	100	40	40.0	0.5472
Anxiety							
No	1695	193	11.4	2954	632	21.4	<0.0001
Yes	11	4	36.4	665	236	35.5	0.9520
Depression							
No	1701	197	11.6	3220	685	21.3	<0.0001
Yes	5	0	0.00	399	183	45.9	0.0406

BZD = benzodiazepine; SD = standard deviation.
* Student *t* test; Chi-squared test.

$P < 0.001$), and when the various subgroups were stratified according to age, the percentage of the BZD users was higher than that of the non-BZD users (Chi-squared test, $P < 0.05$). The percentage of BZD users was higher than that of non-BZD users, even when they did not have comorbidities, such as sleep disorders (20.9% vs 11.3%), dementia (23.5% vs 11.5%), anxiety (21.4% vs 11.4%), or depression (21.3% vs 11.6%; Chi-squared test, $P < 0.001$). Regarding comorbidities, a significantly higher percentage of BZD use was observed in participants with sleep disorders than in those without sleep disorders (29.9% vs 15.4%; Chi-squared test, $P = 0.001$; Table 1).

As mentioned, among the 5325 participants, 1065 were categorized into the epilepsy group and 4260 were categorized into the control group (Figure 1; Table 2). The epilepsy and control groups were similar in age (48.6 ± 18.0 vs 48.5 ± 18.1 years, Student *t* test, $P = 0.90$) and had similar sex ratios (Chi-squared test, $P = 0.99$). The epilepsy group demonstrated a higher proportion of participants with comorbidity history and BZD exposure compared with the control group (Chi-squared test, $P < 0.0001$). Approximately 81.5% and 64.6% of the participants in the epilepsy and control groups, respectively, received BZD during 1996 to 2011 (Table 2).

As shown in Table 3, the aOR of epilepsy in the BZD users was 2.02 (95% CI = 1.68–2.42), indicating that the epilepsy risk demonstrated a higher associations with BZD exposure in BZD users compared with that in non-BZD users. In addition, 55.1% of the participants consumed ≥0.09 DDD of BZD, with an aOR of ≥3.06 for epilepsy, and 56.9% of the participants had >1-week BZD use per year, with an aOR of ≥3.16 for epilepsy. The aOR for epilepsy increased with the DDD of BZD.

TABLE 2. Demographics Characteristics Between Epilepsy and Control Groups

	Controls, N = 4260		Epilepsy, N = 1065		
Variables	**n**	**%**	**n**	**%**	***P* Value**
Sex					0.99
Women	1920	45.1	480	45.1	
Men	2340	54.9	585	54.9	
Age, y					0.99
20–34	1188	27.9	297	27.9	
35–44	856	20.1	214	20.1	
45–54	748	17.6	187	17.6	
55–64	576	13.5	144	13.5	
≥65	892	20.9	223	20.9	
Age, mean (SD), yr*	48.5 (18.1)		48.6 (18.0)		0.90
BZD exposure					<0.0001
No	1509	35.4	197	18.5	
Yes	2751	64.6	868	81.5	
Comorbidity					
Sleep disorders	947	22.2	383	36.0	<0.0001
Dementia	63	1.48	41	3.85	<0.0001
Anxiety	436	10.2	240	22.5	<0.0001
Depression	221	5.2	183	17.2	<0.0001

BZD = benzodiazepine; SD = standard deviation.
* Student *t* test; Chi-squared test.

TABLE 3. Association Between Epilepsy and BZD Exposure Stratified by Dosage and Exposure Day of BZD

Variables	N	Case	Crude OR (95% CI)	Adjusted OR (95% CI)
BZD exposure				
No	1706	197	1.00	1.00
Yes	3619	868	2.42 (2.05–2.86)**	2.02 (1.68–2.42)**
Daily exposure BZD dose				
Non	1706	197	1.00	1.00
<0.01	879	118	1.19 (0.93–1.52)	1.26 (0.99–1.61)
0.01–0.09	937	163	1.61 (1.29–2.02)**	1.74 (1.38–2.20)**
0.09–1.50	901	248	2.91 (2.36–3.58)**	3.06 (2.42–3.88)**
≥1.50	902	339	4.61 (3.77–5.64)**	4.32 (3.38–5.52)**
Increase dose of BZD use (per 100 DDD)	5325	1065	1.04 (1.02–1.06)**	1.03 (1.01–1.04)*
Annual BZD exposure day				
Non	1706	197	1.00	1.00
<2	955	121	1.11 (0.87–1.42)	1.20 (0.94–1.53)
2–7	860	141	1.50 (1.19–1.90)**	1.67 (1.32–2.13)**
8–35	892	233	2.71 (2.19–3.34)**	3.16 (2.49–3.99)**
≥35	912	373	5.30 (4.35–6.47)**	5.60 (4.36–7.18)**
Increase day of BZD use (per 30 d)	5325	1065	1.05 (1.03–1.06)**	1.03 (1.01–1.04)**

Daily exposure BZD dose: the accumulate BZD dose divided by the first BZD exposure date until the index date. Annual BZD exposure day: total BZD exposure day divided by the total follow-up years. Model adjusted for age, sex, and comorbidities of sleep disorders, dementia, and anxiety. BZD = benzodiazepine; CI = confidence interval; DDD = defined daily dose; OR = odds ratio. $*P < 0.01$, $**P < 0.001$.

Compared with that in non-BZD users, the aOR of epilepsy increased to 1.74 (95% CI = 1.38–2.20) and 4.32 (95% CI = 3.38–5.52) for participants on 0.01 to 0.09 and ≥1.50 DDD of BZD, respectively. On average, when the DDD of BZD exposure increased by 100 units, the epilepsy risk increase by 1.03-fold (95% CI = 1.01–1.04, $P = 0.003$). Furthermore, the annual BZD exposure days were significantly associated with epilepsy occurrence (2–7 days: aOR = 1.67, 95% CI = 1.32–2.13; 8–35 days: aOR = 3.16, 95% CI = 2.49–3.99; and ≥35 days: aOR = 5.60, 95% CI = 4.36–7.18). Whenever the annual BZD exposure days increased by 30 days, the epilepsy risk notably increased by 1.03-fold (95% CI = 1.01–1.04, $P < 0.001$; Table 3).

Table 4 shows the association between the BZD use periods before the index date and the epilepsy risk. The participants were classified into 5 subgroups according to the duration of BZD use before the index date: 1 week, 1 month, 3 months, 6 months, and 1 year. The participants using BZD between 1 and 6 months were more likely to exhibit higher epilepsy risk than those using BZD for 1 week and 1 year (1 week: aOR = 3.62, 95% CI = 2.71–4.83; 1 month: aOR = 4.36, 95% CI = 3.57–5.32; 3 months: aOR = 4.56, 95% CI = 3.82–5.44; 6 months: aOR = 4.31, 95% CI = 3.64–5.10; and 1 year: aOR = 3.64, 95% CI = 3.10–4.28). In users who quit BZD for <1 week, the aOR for epilepsy was 13.1 (95% CI = 8.86–19.5). The epilepsy risk dramatically declined in users who quit BZD for >1 month.

TABLE 4. Effects of Different Periods of BZD Use on Epilepsy Risk

BZD Treatment	N	Case	Crude OR (95% CI)	Adjusted OR† (95% CI)
With 1 week prior to index date				
No	5100	943	1.00	1.00
Yes	225	122	5.22 (3.98–6.85)*	3.62 (2.71–4.83)*
With 1 mo prior to index date				
No	4755	769	1.00	1.00
Yes	570	296	5.60 (4.67–6.71)*	4.36 (3.57–5.32)*
With 3 mo prior to index date				
No	4472	655	1.00	1.00
Yes	853	410	5.39 (4.61–6.32)*	4.56 (3.82–5.44)*
With 6 mo prior to index date				
No	4220	581	1.00	1.00
Yes	1105	484	4.88 (4.21–5.66)*	4.31 (3.64–5.10)*
With 1 yr prior to index date				
No	3850	503	1.00	1.00
Yes	1475	562	4.10 (3.56–4.72)*	3.64 (3.10–4.28)*

BZD = benzodiazepine; CI = confidence interval; OR = odds ratio.
† Model adjusted for age, sex, and comorbidities of sleep disorders, dementia, anxiety, and depression. $*P < 0.001$.

TABLE 5. Epilepsy Risk Associated With Different Days After Quitting BZD

Variables	N	Case	Crude OR (95% CI)	Adjusted OR† (95% CI)
Non-BZD exposure	1706	197	1.00	1.00
Days after quitting BZD				
<7	145	99	16.5 (11.3–24.1)*	13.1 (8.86–19.5)*
8–30	71	39	9.34 (5.72–15.20)	7.78 (4.69–12.90)*
31–90	76	29	4.73 (2.91–7.68)*	3.81 (2.30–6.33)*
91–180	113	46	5.26 (3.51–7.87)*	4.20 (2.76–6.41)*
≥180	3214	655	1.96 (1.65–2.33)*	1.65 (1.37–1.99)*
P value for trend	–	–	<0.0001	<0.0001

BZD = benzodiazepine; CI = confidence interval; OR = odds ratio.
† Model adjusted for age, sex, and comorbidities of sleep disorders, dementia, anxiety, and depression. $*P < 0.001$.

Nevertheless, although the users quit BZD for >6 months, the epilepsy risk was still 1.65-fold than did the non-BZD users (Table 5).

DISCUSSION

The results of this population-based case–control study indicated that BZD use was significantly associated with epilepsy occurrence, particularly in the ones who received a higher dose of BZD, prolonged use, or had multiple BZD exposures. A BZD dose ≥0.09 DDD, or BZD exposure for more than 1 week in a year was associated with a high risk of epilepsy. Even for a low dose or exposure, the epilepsy risk was higher for participants with a BZD usage rate of 0.01 to 0.09 DDD and BZD exposure rate of 2 to 7 days per year. The epilepsy risk proportionally increased with the DDD and annual BZD exposure days. These results imply that the BZD threshold dose for developing epileptogenesis is probably considerably lower than our previous assumption. Therefore, the rationale of BZD prescription in daily clinical practice must be reconsidered and a substitute for treating agitation, anxiety, and sleep disorders in the future must be developed, particularly when the global prevalence of BZD use has been high among the elderly population for decades.[8–11]

Typically, 1 mg diazepam at night equals 0.1 DDD of BZD per day according to the definition of the ATC system.[7] A maximum dose of 2 mg/day is recommended for any high-potency BZD if administered for more than 1 week and is not suggested to be taken for more than 30 days.[5,11] However, achieving this goal in current clinical practice is difficult, and BZD overuse is frequently observed in the general population worldwide.[11,12] In the present study, 55.1% of the participants received ≥0.09 DDD of BZD, and 56.9% of them had >1-week exposure per year and may possibly overuse BZD. In addition, although most of the participants were ages 45 years or older, 81.5% of those in the epilepsy group and 64.6% of those in the control group received BZD between 1996 and 2011, indicating that potential BZD overuse exists in the current medical care system. BZDs enhanced GABAergic transmission and possibly caused tolerance, adaptation, and resistance.[13,14] In ones who consume BZD, particularly for sleeping in the night, the mental status may change from a seizure-suppressing status to a relative seizure-promoting status during the interdose daytime. Meanwhile, our participants who abruptly stopped using BZDs had a high OR for epilepsy, and the epilepsy risk rapidly decreased as the number of postquitting days increased. These specifications imply that BZD overuse, sudden withdrawal from BZD use, or reduction of the drug concentration during the interdose period may change the GABA receptor subunit expression in the CNS and result in neurobiological adaptation, altered neuronal function, and increased neuronal hyperexcitability, promoting epilepsy.[4,5,14,15]

The risk of neuronal hyperexcitability for epilepsy occurrence can persist for >6 months after participants quit BZD use. This indicates that the reversal of neuronal hyperexcitability, once developed, is difficult. We intend to design additional laboratory studies involving extensive pharmacokinetic processes for defining a definite safe BZD consumption threshold in the future. Another possible explanation is that patients with epilepsy might present with sleep disorders, depression, anxiety, and other psychiatric symptoms, which are frequently treated using BZD before epilepsy diagnosis, particularly in ones with frontal lobe epilepsy.[16–18] We enrolled participants diagnosed with epilepsy between 2004 and 2011 and analyzed their BZD use since 1996. Participants with a history of neurological or psychiatric disorders and currently using BZD are highly likely to receive electroencephalography.[19,20] However, prolonged delay in epilepsy diagnosis was mostly ruled out in these participants, although the reverse causality could not be ruled out theoretically. Moreover, the possible effects of other medications for CNS were not excluded from the study. For example, antidepressant overdose was reported to induce seizures.[21] Patients with dementia have a high epilepsy risk, and certain dementia drugs, such as donezepil, memantine, and rivastigmeine, possibly increase the seizure risk.[22,23] Nevertheless, the confounding effects should be limited because the NHIRD covers approximately the entire 23 million people in Taiwan under a universal reimbursement policy; moreover, the categorical variables, namely sleep disorders, dementia, depression, and anxiety, were controlled in the analysis.

One of the strengths of the present study is its nationwide population-based design. However, this study has some limitations. First, information regarding smoking habits, alcohol consumption, body mass index or weight, socioeconomic status, and family history were not available in the NHIRD; such information might represent confounding factors and may be associated with BZD use. Specifically, cortical atrophy is related to the duration of alcohol intake and predicts an increased risk for epileptic seizures.[24] Second, we could not obtain the classification and frequency of epilepsy from the participants or their medication use to categorize the subgroups for strengthening the data analysis. The ICD-9-CM code for epilepsy (345) contains different epilepsy types, including different focal and generalized epilepsy types. The main

limitation of this study is that epilepsy was considered a single diagnosis, and the specific epilepsy types were not defined. Different BZD types may exhibit dissimilar associations with localization-related epilepsies, warranting additional in-depth studies in the future. Finally, the diagnoses in the NHIRD claims data are primarily used for administrative affairs with anonymity of the identification numbers. We could not contact the participants directly to confirm the details of their BZD use and drug prescriptions before 1996 in our analysis. However, the data about BZD prescription and epilepsy diagnosis derived during the study period were highly reliable. Several studies have reported high accuracy and validity of diagnoses in the NHIRD conducted according to ICD-9-CM code.[3,25,26] We thus concluded that valuable evidence can be obtained from the current and similar studies.

In conclusion, in this population-based case–control study, we determined a significant association between increased epilepsy occurrence and BZD use, particularly in ones with prolonged BZD use, high BZD dose, and multiple BZD exposure days. Additional large-scale and unbiased population-based studies or randomized control trials that involve examining the relationship between epilepsy occurrence and the use of different BZDs are necessary to support our findings before any conclusion can be deduced.

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