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ORIGINAL RESEARCH

Increased Risk of Sudden Sensorineural Hearing Loss in Patients Receiving Sedative-Hypnotics: A Propensity Score Weighting Cohort Study

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Purpose: Benzodiazepine receptor agonists (BZRAs), including benzodiazepines (BZDs) and Z drugs, are widely prescribed for anxiety and sleep. Therefore, issues of tolerance, dependence and adverse effects are of concern. Recent studies suggested a potential link between BZRAs and hearing problems. However, the actual relationship was still unclear. Accordingly, this study aims to investigate the actual association between BZRA use and risk of sudden sensorineural hearing loss (SSNHL) using population data.

Patients and Methods: This study used the Taiwan Longitudinal Health Insurance Database. 137,277 BZRA users and 1,328,554 nonusers were identified for relevant analyses. We used cohort design with inverse-probability treatment weighting (IPTW) strategy to balance the baseline differences of demographics and comorbidities between two groups. The 5-year incidence of SSNHL was followed. Cox proportional-hazard regression analyses were used to estimate the hazard ratios (HRs).

Results: BZRA users showed an increased 5-year SSNHL risk (adjusted HR: 1.244) after weighting. Subgroup and sensitivity analyses produced consistent results. Notably, SSNHL risk was higher among young BZRA users (adjusted HR: 1.397). BZRA users had the highest SSNHL risk in the first year (adjusted HR: 2.037) after IPTW.

Conclusion: BZRA use elevated the risk of SSNHL, particularly in young adults and in the first year. This emphasises the importance for physicians and policymakers should be aware of the potential hearing difficulties among BZRA users and take necessary examinations.

Keywords: benzodiazepine receptor agonists, drug safety, hearing, sudden sensorineural hearing loss, sedative-hypnotics

Introduction

Benzodiazepine receptor agonists (BZRAs), including benzodiazepines (BZDs) and non-BZDs (Z drugs), are commonly prescribed for anxiety disorders, sleep disorders and epilepsy.[1,2] They are widely used as common psychotropic medications in clinical practice, with 5.2% of adults in the United States aged 18 to 80 being prescribed BZDs.[3] In Switzerland, more females than males use BZRAs and most of them are long-term users (>90 days), with approximately 1.6% taking high doses of BZRAs for a long time.[4] BZRAs mainly act on the γ-aminobutyric acid A ($GABA_A$) receptor, enhancing the inhibitory effect of GABA to produce anxiolytic and sedative effects.[5] Despite their therapeutic benefits, concerns emerge about potential drawbacks such as tolerance, dependence, withdrawal phenomena, cognitive decline and an increased risk of falls and fractures in older populations.[6,7] Consequently, the safety profile of BZRAs has garnered increasing attention. In recent years, increasing reports have highlighted potential neurological dysfunction among BZRA users.[8]

Sudden sensorineural hearing loss (SSNHL) is characterised by a rapid onset of unilateral hearing loss within 72 hours.[9] It can occur at any age but is most common between 43 and 53 years old,[10] with similar incidence rates in men and women.[11] In the United States, the annual incidence of SSNHL is 27 per 100,000, ranging from 11 to 77 per 100,000 across different age groups.[12] Although SSNHL has a significant impact on patients' social and interpersonal lives, its

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exact etiologies remain unclear, but factors such as metabolic disorders, vascular diseases, trauma, tumours and certain medications may contribute to its development.[13,14] Recent studies have suggested a potential link between medication exposure, including bupropion, nortriptyline, and antidepressants, and an increased risk of SSNHL.[15–17] Accordingly, understanding the role of medications in hearing loss is crucial for effectively managing this condition.

Recent basic research has highlighted the crucial role of the GABA receptor in the auditory system and suggested a link between GABA alterations and hearing issues.[18–21] Several clinical studies have also hinted at the potential impact of BZRA on hearing.[22,23] However, conflicting reports exist, with some suggesting that drug abuse, including BZRAs, could contribute to hearing loss or SSNHL.[24–26] Furthermore, a recent systematic review has revealed inconsistent evidence regarding the clinical efficacy of these agents in treating related conditions. Given the close relationship between BZRAs and auditory function, the lack of consensus and the limited large-scale epidemiological studies, this study aimed to investigate the actual relationship between BZRA use and the subsequent risk of SSNHL using a population-based database and a propensity score weighting strategy.

Materials and Methods

Data Source

The data for this population-based study was obtained from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005), which includes claims data for 2 million randomly selected individuals enrolled in the 2005 National Health Insurance (NHI) program in Taiwan. The NHI program, launched in 1995, is a mandatory health insurance system that covers over 99% of Taiwan's residents and reimburses a wide range of healthcare expenses. The NHI database includes claims data and comprehensive details on both outpatient and inpatient services, encompassing medical history, prescriptions, diagnoses, and personal characteristics such as sex, date of birth, residence, monthly insured salary, and insurance information. The NHI program is considered representative of the Taiwanese community. This study was approved by the Institutional Review Board of the Taiwan Tri-Services General Hospital (TSGHIRB C202205001). Given the anonymised and de-identified nature of the data, the requirement for informed consent was waived in accordance with ethical guidelines for secondary data analysis.

Study Sample Selection and BZRA Exposure Definition

The study initially included 1,465,831 residents who had healthcare records between January 1, 2001, and December 31, 2008. To ensure the study focused on an adult population, individuals under 20 years of age were excluded. Additionally, patients with any history of BZRA use or SSNHL prior to the index date were removed to eliminate pre-existing cases that might confound the results. After these exclusions, 137,277 patients with BZRA exposure were identified as the BZRA user group, and 1,328,554 patients without BZRA exposure were categorized as the comparative nonuser group. BZRA exposure was defined based on Anatomical Therapeutic Chemical (ATC) codes for benzodiazepine (N05BA and N05CD) and Z-drugs (N05CF), commonly prescribed for sedative-hypnotic purposes. For BZRA users, the index date was assigned as the date of their first ambulatory care visit involving BZRA treatment. For nonusers, an index date was randomly assigned based on their ambulatory care visits during the study period to establish a comparable timeframe for follow-up.

To address potential confounding due to differences in demographic and health-related factors between BZRA users and nonusers, an inverse probability of treatment weighting (IPTW) approach based on propensity scores was applied. The propensity score model accounted for a range of factors, including age, gender, index year, and specific comorbidities that could influence SSNHL risk: chronic otitis media, hypertension, diabetes mellitus, hyperlipidemia, depression, anxiety, sleep disorders, and head injury. To develop the propensity score model, we used a logistic regression to estimate the likelihood of receiving BZRA. For BZRA users, the weights were calculated as the inverse of the propensity score (1/PS), and for non-users, the weights were calculated as 1/(1-PS).[27] These weights were applied in subsequent analyses to balance the baseline characteristics among groups. This adjustment aimed to balance baseline characteristics and reduce potential biases. The sample selection flowchart is displayed in Figure 1.

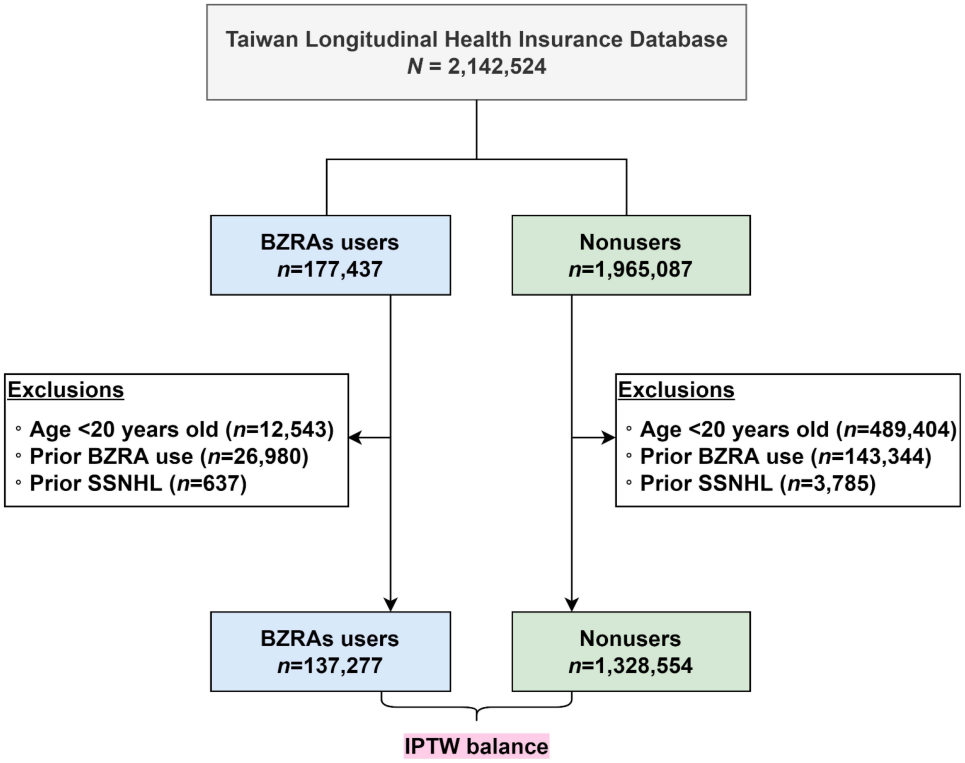

Figure 1 Selection of BZRAs users and nonusers.

Outcome Measures

The aim of this study was to investigate the association between BZRA use and the risk of SSNHL. All patients in the study were followed up for five years from the index date to detect SSNHL occurrence. SSNHL was defined by the International Classification of Diseases, Ninth Revision, Clinical Modification Code 388.2, a standard definition in the research literature.[17,28] Additional analyses were conducted to assess the association between BZRA use and SSNHL risk over varying follow-up periods. Subgroup analyses were also performed in this study.

Statistical Analysis

All statistical analyses in this study were conducted using SAS software (version 9.4; SAS Institute, Cary, NC, USA). Standardised differences were used to compare baseline variables, including demographics and comorbidities, between BZRA users and nonusers. The survival rates were analysed using the Kaplan–Meier method and compared between the two groups using the Log rank test. Cox proportional-hazards regression models were used in both the full cohort analysis and the IPTW cohort analysis to calculate crude and adjusted hazard ratios (HRs) for SSNHL in BZRAs users compared to nonusers. The results were presented as HRs with corresponding 95% confidence intervals (CIs) and a two-sided p-value of 0.05 was considered statistically significant. In this study, after considering effect size, sample size, alpha value and two-tailed detection, the statistical power > 0.9.

Results

The baseline characteristics of the study population are summarised in Table 1. In the full cohort analysis, the average age of BZRA users was higher than that of nonusers (47.89 years vs 44.22 years). BZRA users also had a higher prevalence of hypertension (26.51% vs 19.79%), hyperlipidemia (45.89% vs 34.84%), depression (14.63% vs 4.57%), anxiety (23.84% vs 9.93%) and sleep disorders (32.07% vs 14.33%), with all standardised differences above 0.1. However, after IPTW, no significant differences were found between the two groups in terms of gender, age, chronic otitis media, hypertension, diabetes mellitus, hyperlipidemia, depression, anxiety, sleep disorders and head injury (all

Table 1 Demographics and Comorbidities of Study Population

Variables	Full Cohort (N=1,465,831)					Inverse-Probability Treatment-Weighting (IPTW) Cohort		
	BZRAs Users (n=137,277)		Nonusers (n=1,328,554)		Standardised Difference[a]	BZRAs Users	Nonusers	Standardised Difference[a]
	n	%	n	%		%		
Age (mean ± SD)	47.89 ±16.23		44.22±16.41		0.2481	45.11±15.89	44.24±16.49	0.0534
Sex					−0.0148			−0.0188
Men	62,318	45.40	654,746	49.28		50.76	49.82	
Women	74,959	54.60	673,808	50.72		49.24	50.18	
Comorbidities								
Chronic otitis media	870	0.63	7987	0.60	0.0042	0.66	0.61	0.0075
Hypertension	36,387	26.51	262,906	19.79	0.1598	22.26	20.48	0.0435
Diabetes	15,921	11.60	140,377	10.57	0.0329	11.57	10.68	0.0282
Hyperlipidemia	62,995	45.89	462,927	34.84	0.2265	37.52	35.94	0.0329
Depression	20,080	14.63	60,758	4.57	0.3464	6.42	5.59	0.0349
Anxiety	32,733	23.84	131,926	9.93	0.3780	12.70	11.32	0.0423
Sleep disorders	44,031	32.07	190,406	14.33	0.4299	17.48	16.08	0.0375
Head injury	7811	5.69	80,206	6.04	−0.0148	6.19	6.01	0.0077

Notes: [a]covariates were considered to be balanced between groups if standardised difference < 0.1.
Abbreviations: IPTW, inverse probability of treatment weighting; SD, standard deviation.

standardised differences <0.1). The demographics and comorbidities between BZRA users and nonusers were comparable.

Table 2 summarises the risk of developing SSNHL in the study cohort after a 5-year follow-up. In the 5-year study period, the incidence rates of SSNHL per 1000 person-years in the full cohort were 0.87 and 0.65 among BZRA users and nonusers, respectively. Figure 2 illustrates the SSNHL-free survival curve for BZRA users and nonusers (Log rank test $p < 0.001$). The primary analysis in the full cohort revealed that BZRA users had a significantly higher risk of developing SSNHL over the 5-year follow-up period than nonusers (HR: 1.335, 95% CI: 1.225–1.454). This increased risk persisted even after adjusting for characteristics and comorbidities (adjusted HR: 1.136, 95% CI: 1.041–1.240). Similar results were observed in the IPTW cohort, where BZRA users had a higher risk of SSNHL than nonusers after weighting and adjustment (adjusted HR: 1.244, 95% CI: 1.139–1.358). Additionally, when analyzing BZD and Z-drug users separately, it was found that BZD users had a higher risk of SSNHL than nonusers in the IPTW cohort after adjustments (adjusted HR: 1.307, 95% CI: 1.194–1.431). On the other hand, the risk of SSNHL among Z-drug users was lower than that among nonusers, although this difference was not statistically significant (adjusted HR: 0.725, 95% CI: 0.523–1.004). In the full cohort analysis, low-dose BZRA use was associated with a 30.8% higher crude hazard of 5-year SSNHL events (HR: 1.308, 95% CI: 1.112–1.431), which remained significant after adjustment (adjusted HR: 1.135, 95% CI: 1.052–1.262). Similarly, high-dose BZRA use showed an even greater risk, with a 35.4% increase in crude hazard (HR: 1.354, 95% CI: 1.250–1.516) and an adjusted HR of 1.246 (95% CI: 1.105–1.351). In IPTW cohort analysis, consistent findings were observed, with significant associations between both high and low dose levels and SSNHL risk.

Table 3 presents the results of subgroup analyses. After adjusting for confounders in the IPTW cohort, it was found that BZRA users had a higher risk of SSNHL than nonusers in various subgroups, including men, women, patients under 64 years old, patients with and without diabetes and hyperlipidemia and patients without hypertension, chronic otitis media, depression, anxiety, sleep disorders and head injury. Notably, in the younger population, BZRA users had an increased risk of SSNHL compared to nonusers (adjusted HR: 1.397 for patients aged 39 years or younger and adjusted HR: 1.162 for those aged 40–64 years). However, there was no significant association between BZRA use and SSNHL in

Table 2 Incidence and Hazard Ratio for the 5-Year Risk of Sudden Sensorineural Hearing Loss (SSNHL) Incidence Between BZRA Users and Nonusers

BZRA Use	5-year SSNHL Events Occurrence				Full Cohort Analysis		Inverse-Probability Treatment-Weighting (IPTW) Cohort Analysis	
	n	%	Person-year	Incidence rate per 1000 person-years	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
BZRA users	595	0.43	684,781	0.87	1.335*** (1.225–1.454)	1.136** (1.041–1.240)	1.262*** (1.156–1.377)	1.244*** (1.139–1.358)
Nonusers	4320	0.33	6,632,688	0.65	Reference		Reference	
Different types of BZRAs								
Benzodiazepines (BZD)	542	0.45	595,634	0.91	1.398*** (1.278–1.528)	1.209*** (1.105–1.134)	1.324*** (1.204–1.446)	1.307*** (1.194–1.431)
Z-drugs	53	0.30	89,147	0.59	0.916 (0.699–1.201)	0.655** (0.498–0.861)	0.815 (0.653–1.051)	0.725 (0.523–1.004)
BZRA dosage[b]								
Low-dose BZRA use	252	0.38	298,009	0.85	1.308*** (1.112–1.431)	1.135** (1.052–1.262)	1.298*** (1.054–1.357)	1.258** (1.023–1.287)
High-dose BZRA use	343	0.48	389,772	0.88	1.354*** (1.250–1.516)	1.246** (1.105–1.351)	1.305*** (1.204–1.450)	1.295*** (1.184–1.367)

Notes: [a]adjustment for sex, age, chronic otitis media, hypertension, diabetes mellitus, hyperlipidemia, depression, anxiety, sleep disorders, head injury. [b]The cumulative dose of BZRA was calculated, and the median was used to divide it into two groups for analysis. **P<0.01 ***P<0.001.
Abbreviations: IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence intervals.

the elderly population. Furthermore, among patients without chronic otitis media, depression, anxiety, sleep disorders or head injuries, BZRA use was found to potentially increase the risk of SSNHL. Nevertheless, there was a trend toward a lower risk of SSNHL with BZRA use in patients with these conditions, although the results did not reach statistical significance.

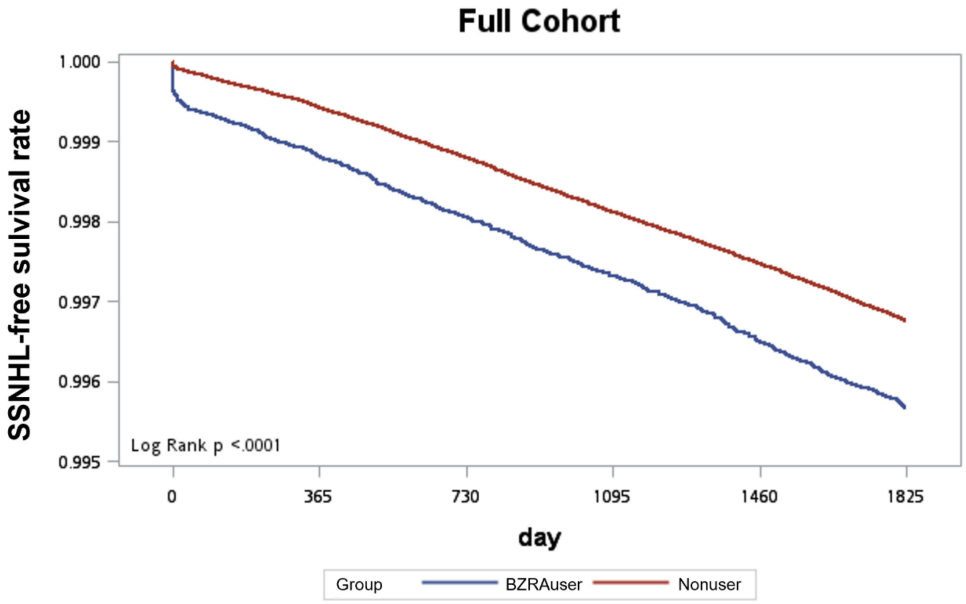

Figure 2 Sudden sensorineural hearing loss-free survival curve between BZRA users and nonusers.

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Table 3 Association Between BZRAs and Following Sudden Sensorineural Hearing Loss (SSNHL) Incidence According to Different Subgroups

Subgroups	Full Cohort Analysis					Inverse-Probability Treatment-Weighting (IPTW) Cohort Analysis	
	n (%)	Person-Year	Incidence Rate per 1,000 person-years	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
				BZRA Users vs Nonusers		BZRA Users vs Nonusers	
Sex							
Men	2563 (0.35)	3,674,362	0.70	1.344*** (1.188–1.521)	1.156* (1.019–1.312)	1.259*** (1.114–1.424)	1.244*** (1.100–1.407)
Women	2352 (0.32)	3,642,807	0.65	1.337*** (1.187–1.507)	1.125 (0.997–1.271)	1.266*** (1.117–1.435)	1.250*** (1.103–1.417)
Age group							
≤ 39 years old	1328 (0.21)	3,226,472	0.41	1.402** (1.169–1.681)	1.264* (1.049–1.524)	1.442*** (1.222–1.701)	1.397*** (1.184–1.649)
40–64 years old	2560 (0.41)	3,096,709	0.83	1.190** (1.059–1.339)	1.070 (0.950–1.206)	1.176** (1.042–1.328)	1.162* (1.029–1.312)
≥ 65 years old	1027 (0.52)	993,988	1.00	1.180 (0.990–1.406)	1.138 (0.953–1.359)	1.147 (0.942–1.397)	1.509 (0.991–2.298)
Hypertension							
Yes	1637 (0.55)	1,492,357	1.10	1.006 (0.868–1.166)	0.982 (0.845–1.141)	0.984 (0.837–1.156)	1.024 (0.871–1.204)
No	3278 (0.28)	5,824,812	0.56	1.448*** (1.304–1.609)	1.214*** (1.089–1.352)	1.393*** (1.255–1.547)	1.340*** (1.207–1.488)
Diabetes							
Yes	1005 (0.64)	779,027	1.29	1.151 (0.949–1.397)	1.169 (0.961–1.423)	1.214* (1.003–1.469)	1.249** (1.032–1.511)
No	3910 (0.30)	6,538,142	0.60	1.369*** (1.244–1.506)	1.117* (1.012–1.231)	1.261*** (1.142–1.391)	1.233*** (1.117–1.361)
Hyperlipidemia							
Yes	2567 (0.49)	2,623,518	0.98	1.119 (0.998–1.254)	1.073 (0.956–1.205)	1.141* (1.008–1.291)	1.173* (1.036–1.327)
No	2348 (0.25)	4,693,651	0.50	1.427*** (1.254–1.625)	1.225** (1.073–1.400)	1.375*** (1.214–1.557)	1.316*** (1.162–1.490)
Chronic otitis media							
Yes	66 (0.75)	44,123	1.50	0.753 (0.303–1.874)	0.677 (0.270–1.700)	0.514 (0.177–1.490)	0.534 (0.184–1.551)
No	4849 (0.33)	7,273,046	0.67	1.343*** (1.232–1.464)	1.144** (1.048–1.249)	1.273*** (1.165–1.390)	1.254*** (1.148 −1.369)
Depression							
Yes	393 (0.49)	403,200	0.97	0.860 (0.678–1.091)	0.855 (0.673–1.087)	0.776 (0.551–1.094)	0.930 (0.658–1.315)
No	4522 (0.33)	6,913,969	0.65	1.371*** (1.250–1.504)	1.187*** (1.081–1.303)	1.310*** (1.196–1.434)	1.271*** (1.161–1.392)
Anxiety							
Yes	900 (0.55)	821,003	1.10	0.812* (0.682–0.967)	0.818* (0.686–0.976)	0.814 (0.648–1.023)	0.871 (0.692–1.096)
No	4015 (0.31)	6,496,166	0.62	1.424*** (1.291–1.572)	1.268*** (1.147–1.401)	1.369*** (1.245–1.505)	1.322*** (1.202–1.454)
Sleep disorders							
Yes	1171 (0.50)	1,169,227	1.00	0.827* (0.707–0.966)	0.817* (0.698–0.956)	0.833 (0.681–1.020)	0.879 (0.718–1.076)
No	3744 (0.30)	6,147,942	0.61	1.490*** (1.344–1.652)	1.327*** (1.196–1.473)	1.408*** (1.277–1.552)	1.352*** (1.226–1.490)
Head injury							
Yes	348 (0.40)	439,260	0.79	1.149 (0.81–1.629)	0.973 (0.682–1.39)	1.193 (0.859–1.657)	1.203 (0.865–1.671)
No	4567 (0.33)	6,877,908	0.66	1.349*** (1.235–1.474)	1.148** (1.049–1.257)	1.267*** (1.157–1.387)	1.245*** (1.137–1.364)

Notes: [a]adjustment for sex, age, chronic otitis media, hypertension, diabetes mellitus, hyperlipidemia, depression, anxiety, sleep disorders, head injury. *P<0.05 **P<0.01 ***P<0.001.
Abbreviations: IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence intervals.

Table 4 BZRA Use and Following Risk of Sudden Sensorineural Hearing Loss (SSNHL) According to Different Follow-Up Periods

SSNHL Events	Full Cohort Analysis	Inverse-Probability Treatment-Weighting (IPTW) Cohort Analysis
	BZRAs Users vs Nonusers	
1-year study period		
Crude HR (95% CI)	2.061*** (1.740–2.442)	2.063*** (1.742–2.442)
Adjusted HR[a] (95% CI)	1.754*** (1.473–2.088)	2.037*** (1.720–2.411)
2-year study period		
Crude HR (95% CI)	1.624*** (1.427–1.848)	1.614*** (1.418–1.836)
Adjusted HR[a] (95% CI)	1.374*** (1.203–1.569)	1.592*** (1.399–1.811)
3-year study period		
Crude HR (95% CI)	1.425*** (1.278–1.590)	1.357*** (1.214–1.517)
Adjusted HR[a] (95% CI)	1.189** (1.063–1.330)	1.338*** (1.197–1.496)
4-year study period		
Crude HR (95% CI)	1.389*** (1.263–1.528)	1.318*** (1.195–1.453)
Adjusted HR[a] (95% CI)	1.172** (1.063–1.292)	1.299*** (1.178–1.432)
5-year study period		
Crude HR (95% CI)	1.335*** (1.225–1.454)	1.262*** (1.156–1.377)
Adjusted HR[a] (95% CI)	1.136** (1.041–1.240)	1.244*** (1.139–1.358)

Notes: [a]adjustment for sex, age, chronic otitis media, hypertension, diabetes mellitus, hyperlipidemia, depression, anxiety, sleep disorders, head injury. **P<0.01 ***P<0.001.

Table 4 shows the association between BZRA use and SSNHL risk over different follow-up periods. The results show that after controlling for confounders in the IPTW cohort, the highest risk of SSNHL was detected in the 1-year study period (adjusted HR: 2.037). Additionally, the SSNHL risk remained significant over 2 to 5 follow-up periods (adjusted HR: 1.592 for 2-year study period, adjusted HR: 1.338 for 3-year study period, adjusted HR: 1.299 for 4-year study period and adjusted HR: 1.244 for 4-year study period).

Discussion

This study found that BZRA use was associated with a higher risk of SSNHL after adjusting and weighting for confounders. Subgroup analyses also showed consistent findings across most subgroups, including men, women and patients with or without certain comorbidities. Few human studies have focused on the relationship between BZRA use and the risk of SSNHL and the existing findings are inconsistent.

To date, some case reports have suggested that drug abuse, including BZRAs, may contribute to hearing loss or SSNHL.[24–26] For instance, a case report in Philadelphia described a patient aged 18 years who experienced bilateral, moderately severe SSNHL after two days of polysubstance abuse, including BZDs, alcohol, heroin, etc.[24] In addition, a systematic review has revealed hearing loss and abnormal auditory function were observed in individuals using illicit drugs or their combinations with other substances.[25] Nevertheless, some researchers have suggested that BZD may play a role in managing hearing problems and have conducted studies on the topic. For example, several clinical studies with small sample sizes have shown that BZDs or related combinations could alleviate tinnitus symptoms.[29,30] However, a crossover randomised clinical trial involving 36 patients with tinnitus found that daily alprazolam did not significantly improve tinnitus compared to a placebo.[31] Overall, there is no consistent evidence supporting the use of BZRAs in treating auditory disorders. Accordingly, the American Academy of Otolaryngology-Head and Neck Surgery guidelines do not recommend the use of antianxiety medications for treating tinnitus, as clinical trials have not demonstrated positive effects.[32]

Our study found an increased risk of SSNHL in BZRA users. The exact mechanism behind this association remains unclear, as there is limited research on the topic. However, growing evidence suggests that GABA in the human auditory cortex may play a role in hearing.[19,33–35] Previous study have suggested that alterations in GABAergic systems, such as

down-regulation of K + –Cl– co-transporter isoform 2 (KCC2), may lead to central auditory dysfunction after auditory trauma.[36] According to studies, BZRA activates GABA A receptors, which are widely distributed throughout the central nervous system (CNS), mainly in the cerebral cortex, resulting in a widespread suppression of neuronal activity.[37–40] Therefore, it is possible that alterations in GABA receptors in the auditory system could be a potential mechanism for the increased risk of SSNHL in BZRA users.[18–21] Accordingly, BZRAs are known to enhance the inhibitory neurotransmitter in the central nervous system,[41] which can be beneficial for anxiety and sleep disorders. However, this modulation may lead to neurotransmitter imbalances in the auditory pathway, further disrupting the transmission of auditory signals and potentially leading to SSNHL. Additionally, sleep's role in cognition and IADLs may also influence our findings, as sleep disturbances impact cognitive function and could affect cooperation in assessments, including auditory tests.[42,43] Without detailed cognitive testing, the observed auditory loss might stem from cognitive changes affecting participant engagement, rather than directly from BZRA use, suggesting an area for future research.

Our study found that BZD use may increase the risk of SSNHL, while Z drugs were not associated with SSNHL. This difference could be attributed to the pharmacological differences between the two types of medications. BZDs bind non-selectively to $GABA_A$ receptors containing a γ2 subunit, while Z drugs bind with higher relative affinity to α1-containing receptors.[44] These different pharmacological pathways may influence neurotransmitter balance and impact the transmission of auditory signals. Additionally, it is noteworthy that BZRA users in the young population had a higher risk of SSNHL than nonusers. However, there was no association between BZRA use and SSNHL in the elderly population. Although the exact reason remains unclear, a recent study has suggested that the auditory system undergoes changes in response to the gradual loss of input with increasing age.[34] This could explain the differing incidence of SSNHL between young and elderly populations. The observed variation in SSNHL risk associated with BZRA use between different subgroups may reflect underlying physiological and behavioral differences. For example, in participants without stroke-related risk factors (eg, hypertension, diabetes),[45,46] the effects of BZRAs on auditory health may be more apparent due to the absence of competing vascular risks that could confound SSNHL incidence. This study found that BZRA users with anxiety or sleep issues had a decreased risk of SSNHL than users without these conditions. However, the results were not statistically significant, limiting the capacity to extrapolate the findings. A likely explanation for this finding is that increased sleep quality among BZRA users with sleep disorders may have a preventive impact, as poor sleep has been linked to detrimental effects on vascular and neurological health, potentially raising the incidence of SSNHL. This is congruent with the existing literature, which emphasizes the negative impact of sleep disturbances on general health, particularly in auditory and brain networks. However, because the observed differences are not statistically significant, this hypothesis remains uncertain. Additionally, age-related differences might stem from variations in drug metabolism, cumulative exposure, or baseline susceptibility to auditory damage.[47] For younger individuals, lifestyle factors or lower baseline SSNHL risk may amplify the relative contribution of BZRAs, while older adults may have other dominant risk factors that mask the BZRA effect. These findings highlight the importance of considering age and comorbidities when assessing medication risks and emphasize the need for further research to elucidate the mechanisms linking BZRAs, comorbidities, and SSNHL risk.

This study has several strengths. First, it is the first cohort study to use a large health database to investigate the relationship between BZRA use and the risk of SSNHL, thereby reducing selection bias in observational studies. Second, by focusing on new users, the study minimised the impact of prior drug exposure, establishing a causal relationship between BZRA use and SSNHL occurrence. Third, the study employed the IPTW analysis method to mitigate the impact of confounding factors. However, there are several limitations to consider. First, the NHI database lacks lifestyle information (eg alcohol consumption and smoking), laboratory data and family history, which could influence SSNHL occurrence. Additionally, environmental factors, such as noise exposure, were not considered in this study. This may result in residual confounding. Second, this study did not consider other medications that may affect hearing, but we identified potential comorbidities in relevant analyses to reduce potential bias. This study further used the IPTW approach to eliminate potential impacts. Third, this study was conducted using data from Taiwan's NHI database, which may limit the generalizability of our findings to other populations and healthcare systems. Finally, the NHI database cannot specify whether SSNHL is unilateral or bilateral.

Conclusion

This is the first epidemiological study to find an association between BZRA use and an increased risk of SSNHL, even after adjusting and weighting for confounders. Notably, young adults who used BZRA had a higher risk of SSNHL than nonusers, while such an association was not observed in older adults. The highest risk of SSNHL was detected in the 1-year follow-up period. Medical professionals and policymakers should be aware of the potential hearing issues among BZRA users and ensure appropriate care. Further studies are warranted to explore the potential mechanisms linking BZRA use to SSNHL risk.

Abbreviations

BZRA, benzodiazepine receptor agonists; SSNHL, sudden sensorineural hearing loss; aORs, adjusted hazard ratios; CI, confidence intervals; GABA, gamma-aminobutyric acid; IPTW, inverse probability of treatment weighting; NHI, National Health Insurance; ORs, crude odds ratios; SDiff, standardized difference.

Data Sharing Statement

The data analyzed in this study was obtained from the Health and Welfare Data Science Center. Requests to access these datasets should be directed to the Health and Welfare Data Science Center, Department of Statistics, Ministry of Health and Welfare, Taiwan, http://dep.mohw.gov.tw/DOS/np-2497-113.htm.

Ethics Approval

This study was approved by the Institutional Review Board of the Taiwan Tri-Services General Hospital (TSGHIRB C202205001). This study complies with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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