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ORIGINAL RESEARCH

Association Between Non-Benzodiazepine Hypnotics and Tinnitus: A Nationwide Cohort Study in Taiwan

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Purpose: Non-benzodiazepine hypnotics, commonly known as Z-drugs, are widely prescribed for conditions such as insomnia, anxiety, and epilepsy. Emerging evidence suggests that these agents may influence auditory function and may be associated with tinnitus, potentially through their modulation of GABAA receptors. However, existing research findings on this association remain inconsistent. The objective of this study was to examine the potential association between the use of Z-drugs and the subsequent risk of incident tinnitus.

Patients and Methods: This study was conducted using the Taiwan Longitudinal Health Insurance Database. The exposure cohort was composed of all beneficiaries who were prescribed a Z-drug during the study period. The comparison cohort was selected from beneficiaries without any prescription history for Z-drugs during the same timeframe. The primary outcome was the risk of tinnitus within a 5-year follow-up period. To minimize potential confounding, propensity score matching was applied, followed by Cox proportional hazards regression analyses to calculate hazard ratios (HRs) comparing Z-drug users with nonusers.

Results: 16,225 patients were identified as Z-drug users, while 1,370,776 were classified as nonusers. Over the 5-year period, Cox proportional hazards regression analysis revealed that Z-drug users had a higher risk of developing tinnitus compared to nonusers (adjusted HR: 1.501; 95% CI: 1.423–1.583). After propensity score matching, this association remained significant (adjusted HR: 1.496; 95% CI: 1.377–1.624). Furthermore, a consistent association between Z-drug use and tinnitus was observed across most subgroups.

Conclusion: The study suggests that the use of Z-drugs, the most prescribed psychoactive drugs globally, may be associated with an increased risk of developing tinnitus. Limitations include the potential for residual confounding and misclassification inherent to claims-based data. Clinicians should consider this potential association when prescribing Z-drugs.

Keywords: non-benzodiazepine hypnotics, Z-drugs, tinnitus, hearing

Introduction

Benzodiazepine receptor agonists (BZRAs), including benzodiazepines and Z-drugs, are the most prescribed psychoactive drugs globally.[1–3] The annual prevalence of the use of any anxiolytic–hypnotic drug is 5.2% for adults in the United States and approximately 20% in Taiwan.[1,4] BZRAs are commonly used to treat insomnia, anxiety, panic disorder, and epilepsy in psychiatric settings because of their sedative, anxiolytic, hypnotic, anticonvulsant, and muscle relaxant effects, which are achieved by improving the actions of brain gamma-aminobutyric acid type A (GABAA) receptors.[5,6] Remarkably, increasing evidence suggests that GABAA receptors play a role in auditory function, and

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Z-drugs, which exhibit selective affinity for the α_1 subunit, may have distinct influences on this system compared to traditional benzodiazepines.[7]

Tinnitus is a prevalent medical symptom with potential debilitating effects and is characterized by the perception of sound without an external stimulus.[8] Studies on the prevalence of tinnitus, primarily conducted in Western Europe and the USA, although with methodological limitations, have reported wide-ranging estimates of 10–15% among adults.[7] Most previous studies conducted in England, the USA, Norway, Egypt, Japan, and Nigeria have also suggested similar prevalence rates.[9–12] Although tinnitus may affect several patients and contribute to their poor quality of life,[13,14] there is a lack of sufficient effective pharmaceutical treatments, and the etiologies are also unclear. To date, tinnitus and hearing problems are recognized as multifactorial conditions with numerous risk factors, including hypertension, head trauma, depression, and noise exposure.[1,15] Some studies have suggested that inappropriate medication exposure is a common risk factor for ototoxicity and induces hearing loss.[16,17] Furthermore, some medications, such as salicylates, aminoglycoside antibiotics, and antidepressants, have been linked to hearing impairment and tinnitus.[16–19] These data emphasize a critical issue regarding drug-induced tinnitus.

Previous experimental research has identified the significant involvement of GABAA receptors in auditory functions.[7] For instance, Ashton et al found that reduced GABAA receptor density was associated with increased excitability in the temporal lobe, while Daftary et al showed that disrupted benzodiazepine receptor function in the temporal lobe may contribute to the pathophysiology of chronic severe tinnitus.[20,21] These findings support the rationale for investigating the association between BZRAs and auditory dysfunction. Although our prior study demonstrated an association between BZRA use and sudden sensorineural hearing loss,[22] tinnitus represents a distinct neurological phenomenon with potentially more persistent effects on quality of life. While both Z-drugs and traditional benzodiazepines are classified as BZRAs, they differ in their pharmacological profiles. Z-drugs exhibit high selectivity for the α_1 subunit of the GABAA receptors, which is primarily responsible for hypnotic effects.[7] This α_1 subunit affinity promotes sedation while producing minimal anxiolytic, muscle-relaxant, or cognitive side effects compared to benzodiazepines.[21,23,24] Given the growing use of Z-drugs and the lack of dedicated large-scale investigations into their auditory safety, a substantial evidence gap remains.

Therefore, considering the inconsistent actual relationship between BZRA and tinnitus in humans and to further understand the effects of Z-drugs on tinnitus, this cohort study examined the association between BZRA use and the subsequent risk of tinnitus using population-based data and a propensity score matching design. The strategy of propensity score matching can efficiently minimize potential confounding due to the imbalance of comorbidities between BZRA users and nonusers.

Materials and Methods

Data Source

This study received ethical approval from the Tri-Service General Hospital's Institutional Review Board (C202205001). A waiver of informed consent was granted because the study relied exclusively on de-identified secondary data. The data were drawn from the Longitudinal Health Insurance Database 2005 (LHID2005), managed by the Health and Welfare Data Science Center (HWDC, MOHW). This database contains the records of 2 million individuals randomly chosen from the National Health Insurance (NHI) registry in 2005. The findings are generalizable to the Taiwanese population, as the NHI program provides healthcare coverage to more than 99% of the nation's 23 million citizens. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Sample Selection and Z Drug Exposure Definition

This cohort study initially included 1,967,854 Taiwanese residents from LHID2005 between January 1, 2001 and December 31, 2010. Then, to restrict the analysis to an adult population, individuals younger than 20 years of age were excluded from the study cohort. Patients with a history of any Z-drug usage (including zopiclone, zolpidem, zaleplon, or eszopiclone) or tinnitus before the index date were also excluded. A total of 16,225 patients who were exposed to Z-drugs were identified as Z-drug users in this study. Z-drug usage was identified using the Anatomical

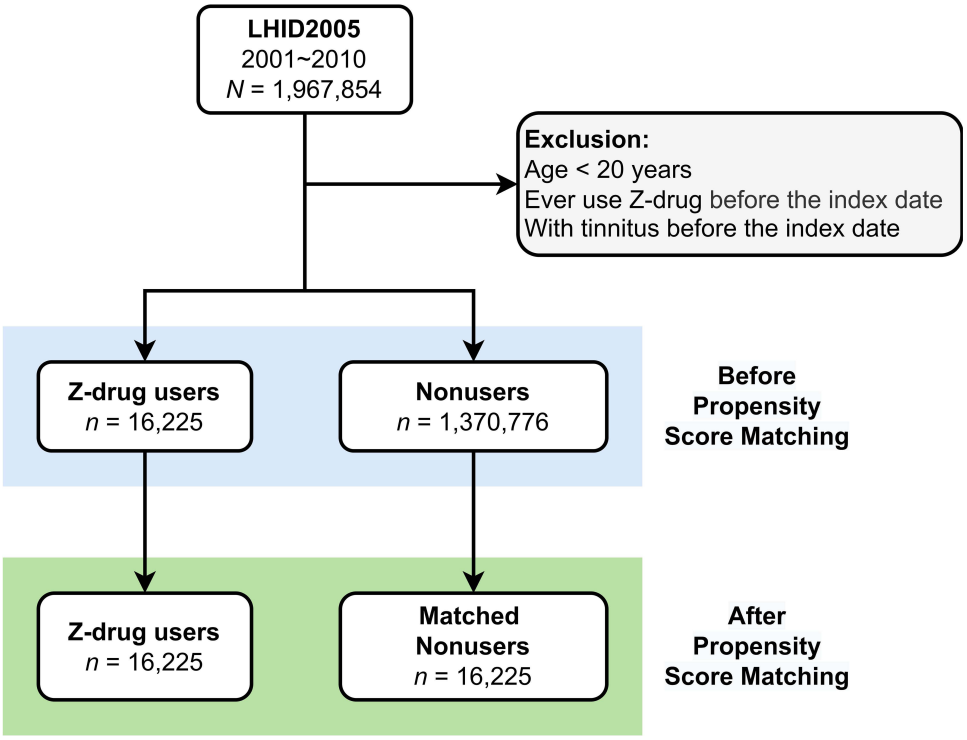

Figure 1 Study sample selection.

Therapeutic Chemical codes of N05CF. In contrast, 1,370,776 patients who were not exposed to any Z-drugs during the study period were classified as nonusers in this study. The date of the first ambulatory care visit with Z-drug treatment was used as the index date for Z-drug users, and nonusers were randomly assigned the date of the ambulatory care visit as the index date.

To eliminate the imbalance of documented confounders between Z-drug users and nonusers, this study further adopted the propensity score matching strategy to minimize confounding effects and reduce bias commonly associated with observational studies. Propensity scores were estimated using a logistic regression model based on demographic characteristics and comorbidities, followed by 1:1 greedy nearest-neighbor matching without replacement, using a caliper width of 0.1. After propensity score matching, the study cohort consisted of 32,450 patients, including 16,225 Z-drug users and 16,225 matched nonusers (Figure 1).

Outcome Measures

This study investigated the association between Z-drug use and the subsequent risk of developing tinnitus. All subjects were followed for a 5-year period from their index date to identify the first diagnosis of tinnitus. The primary outcome, incident tinnitus, was defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 388.3. Potential confounders considered in this study included demographic characteristics (age and sex) and comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, depression, anxiety, chronic otitis media, sleep disorders, and head injury. In addition, several subgroup analyses were conducted to assess the consistency of the association between Z-drug exposure and tinnitus risk across different demographic and clinical subgroups. Specifically, the analysis was stratified by age, which was categorized into three groups: ≤39, 40–64, and ≥65 years.

Statistical Analysis

We performed all statistical analyses using SAS software (version 9.4; SAS Institute, Cary, NC, USA). To evaluate the balance of baseline characteristics, such as demographics and comorbidities, between Z-drug users and nonusers, we calculated standardized differences (SDiffs) and visualized the covariate balance before and after matching using a Love

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plot (Supplementary Figure 1). The association between Z-drug use and the risk of tinnitus was estimated using Cox proportional hazards regression models. Both crude and adjusted hazard ratios (HRs) were calculated, with the adjusted models incorporating all potential confounders listed above, including demographic factors and comorbidities. Statistical significance was set at a two-tailed p-value of less than 0.05.

Several sensitivity analyses were conducted to assess the robustness of our findings. First, to reduce outcome misclassification, the primary analysis was repeated with tinnitus diagnoses restricted to those made by otolaryngologists. Second, a dose–response relationship was evaluated by stratifying cumulative defined daily dose (cDDD) of Z-drugs into quartiles and repeating the analysis in each stratum. Third, inverse probability of treatment weighting (IPTW) using the stabilized propensity score was applied. Finally, burn injuries were analyzed as a negative control outcome to assess potential unmeasured confounding.

Results

Table 1 shows the distribution of demographic characteristics and comorbidities between Z-drug users and nonusers. Before propensity score matching, 16,225 Z-drug users and 1,370,776 nonusers were included. The mean age of Z-drug users and nonusers was 50.21 ± 16.79 and 43.62 ± 16.20 years, respectively. The demographic characteristics and comorbidities were markedly different between the two groups. After propensity score matching, no significant differences were observed between Z-drug users and matched nonusers in all documented demographics and comorbidities.

Table 2 shows the 5-year risk of developing tinnitus among Z-drug users and nonusers before and after propensity score matching. Before propensity score matching, 8.55% of Z-drug users and 5.89% of nonusers had experienced tinnitus. The absolute risk difference in the full cohort was 2.66%. The Cox proportional hazards regression analysis

Table 1 Distribution of Demographics and Comorbidities in Selected Sample Before and After Propensity Score Matching

Variables	Before Propensity Score Matching			After Propensity Score Matching		
	Z-Drug Users (*n*=16225)	Nonusers (*n*=1370776)	Stdiff [a]	Z-Drug Users (*n*=16225)	Nonusers (*n*=16225)	Stdiff [a]
	n (%)			*n* (%)		
Age (mean±SD)	50.21±16.79	43.62±16.20	0.3994	50.21±16.79	50.53±16.86	−0.0192
Gender			0.1922			0.0251
Male	6580 (40.55)	691,988 (50.48)		6580 (40.55)	6554 (40.39)	
Female	9645 (59.45)	678,788 (49.52)		9645 (59.45)	9671 (59.61)	
Comorbidities						
Chronic otitis media			0.0173			0.0047
Yes	27 (0.17)	1412 (0.1)		27 (0.17)	24 (0.15)	
No	16,198 (99.83)	1,369,364 (99.9)		16,198 (99.83)	16,201 (99.85)	
Hypertension			0.3723			−0.0094
Yes	4177 (25.74)	157,599 (11.5)		4177 (25.74)	4244 (26.16)	
No	12,048 (74.26)	1,213,177 (88.5)		12,048 (74.26)	11,981 (73.84)	
Diabetes			0.2297			−0.0017
Yes	1920 (11.83)	74,377 (5.43)		1920 (11.83)	1929 (11.89)	
No	14,305 (88.17)	1,296,399 (94.57)		14,305 (88.17)	14,296 (88.11)	
Hyperlipidemia			0.2266			0.0025
Yes	1930 (11.9)	75,972 (5.54)		1930 (11.9)	1917 (11.82)	
No	14,295 (88.1)	1,294,804 (94.46)		14,295 (88.1)	14,308 (88.18)	
Depression			0.2640			0.0042
Yes	1117 (6.88)	22,021 (1.61)		1117 (6.88)	1100 (6.78)	
No	15,108 (93.12)	1,348,755 (98.39)		15,108 (93.12)	15,125 (93.22)	

(*Continued*)

Table 1 (Continued).

Variables	Before Propensity Score Matching			After Propensity Score Matching		
	Z-Drug Users (*n*=16225)	Nonusers (*n*=1370776)	Stdiff [a]	Z-Drug Users (*n*=16225)	Nonusers (*n*=16225)	Stdiff [a]
	n (%)			*n* (%)		
Anxiety			0.1482			0.0251
Yes	415 (2.56)	9456 (0.69)		415 (2.56)	353 (2.18)	
No	15,810 (97.44)	1,361,320 (99.31)		15,810 (97.44)	15,872 (97.82)	
Sleep disorders			0.4252			−0.0035
Yes	2921 (18)	65,628 (4.79)		2921 (18.00)	2943 (18.14)	
No	13,304 (82)	1,305,148 (95.21)		13,304 (82.00)	13,282 (81.86)	
Head injury			0.0909			0.0291
Yes	335 (2.06)	13,124 (0.96)		335 (2.06)	271 (1.67)	
No	15,890 (97.94)	1,357,652 (99.04)		15,890 (97.94)	15,954 (98.33)	

Notes: [a] Covariates were balanced between groups if standardized difference < 0.1.
Abbreviations: SD, standard deviation; Stdiff, standardized difference.

Table 2 5-Year Risk of Tinnitus in Z-Drug Users and Nonusers Before and After Propensity Score Matching

5-Year Occurrence of Tinnitus	Z-Drug Users	Nonusers
Before propensity score matching		
Number of tinnitus patients (%)	1388 (8.55)	80,738 (5.89)
Crude HR (95% CI)	1.964 (1.863–2.072)***	1.000
Adjusted HR (95% CI)	1.501 (1.423–1.583)***	1.000
IPTW HR (95% CI)	1.742 (1.645–1.844)***	1.000
IPTW adjusted HR (95% CI)	1.695 (1.601–1.794)***	1.000
After propensity score matching		
Number of tinnitus patients (%)	129 (7.95)	80 (4.94)
Crude HR (95% CI)	1.491 (1.373–1.619)***	1.000
Adjusted HR (95% CI)	1.496 (1.377–1.624)***	1.000

Notes: Adjustment for sex, age, chronic otitis media, hypertension, diabetes mellitus, hyperlipidemia, depression, anxiety, sleep disorders, head injury. *** p<0.001.

showed that Z-drug use was associated with a 96.4% higher risk of tinnitus compared with nonuse (crude HR: 1.964; 95% CI: 1.863–2.072; $p < 0.001$). After adjusting for demographic characteristics and comorbidities, the adjusted HR for tinnitus among Z-drug users was 1.501 (95% CI, 1.423–1.583, $p < 0.01$) compared with that among nonusers. Moreover, after propensity score matching, 7.95% of Z-drug users and 4.94% of nonusers were diagnosed with tinnitus. The absolute risk difference in the matched cohort was 3.01%. In the matched cohort, the Cox regression analysis indicated a higher risk of tinnitus associated with Z-drug use compared with nonuse (crude HR: 1.491; 95% CI: 1.373–1.619; $p < 0.001$), and this association remained statistically significant after adjustment (adjusted HR: 1.496; 95% CI: 1.377–1.624; $p < 0.001$). Consistent findings were observed in the IPTW analysis, where Z-drug use remained significantly associated with an increased risk of tinnitus (IPTW-adjusted HR: 1.695; 95% CI: 1.601–1.794). The remaining sensitivity analyses, including restricting tinnitus diagnoses to those made by otolaryngologists, and evaluating a dose–response relationship by stratifying cumulative defined daily dose, also consistently demonstrated significantly higher hazards of tinnitus among Z-drug users (Table 3). These results support the robustness of our findings. This study also included burn injury as a negative control outcome and conducted the corresponding analyses (Supplementary Table 1). The results indicated no association between Z-drug use and the risk of burn injury.

Table 3 Sensitivity Analyses of the Association Between z-Drug Use and Risk of Tinnitus

Variables	Before Propensity Score Matching		After Propensity Score Matching	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Cumulative dose				
Lowest CDDD group	1.670*** (1.499–1.861)	1.509*** (1.354–1.681)	1.269** (1.120–1.438)	1.386*** (1.221–1.573)
Lower-middle CDDD group	1.913*** (1.712–2.138)	1.587*** (1.420–1.774)	1.454*** (1.279–1.652)	1.475*** (1.297–1.676)
Upper-middle CDDD group	2.202*** (2.030–2.388)	1.663*** (1.533–1.804)	1.668*** (1.505–1.849)	1.591*** (1.435–1.764)
Highest CDDD group	2.012*** (1.722–2.351)	1.535*** (1.313–1.794)	1.528*** (1.292–1.807)	1.438*** (1.214–1.704)
Otolaryngologist diagnosis only	1.197*** (1.124–1.275)	1.131*** (1.062–1.205)	1.157** (1.049–1.275)	1.160** (1.052–1.279)

Notes: 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 Z-Drug Use and Risk of Tinnitus According to Different Subgroups

Subgroups	Before Propensity Score Matching		After Propensity Score Matching	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Sex				
Male	2.097*** (1.923–2.287)	1.545*** (1.416–1.686)	1.559*** (1.361–1.787)	1.564*** (1.365–1.792)
Female	1.823*** (1.704–1.95)	1.476*** (1.379–1.579)	1.452*** (1.309–1.611)	1.457*** (1.313–1.615)
Age group				
≤ 39 years	2.290*** (2.044–2.566)	1.989*** (1.773–2.231)	2.011*** (1.654–2.445)	2.009*** (1.652–2.443)
40–64 years	1.718*** (1.596–1.849)	1.503*** (1.396–1.618)	1.445*** (1.291–1.618)	1.441*** (1.287–1.613)
≥ 65 years	1.397*** (1.258–1.551)	1.306*** (1.176–1.451)	1.316** (1.127–1.537)	1.311* (1.122–1.531)
Sleep disorders				
Yes	1.273*** (1.134–1.428)	1.260*** (1.123–1.414)	1.252** (1.059–1.48)	1.267** (1.072–1.498)
No	1.949*** (1.835–2.07)	1.567*** (1.475–1.664)	1.574*** (1.431–1.73)	1.574*** (1.431–1.73)
Chronic otitis media				
Yes	0.568 (0.141–2.288)	0.426 (0.104–1.751)	0.875 (0.123–6.216)	0.517 (0.033–8.072)
No	1.969*** (1.867–2.076)	1.508 *** (1.429–1.591)	1.492*** (1.374–1.621)	1.498*** (1.379–1.626)
Hypertension				
Yes	1.404*** (1.274–1.548)	1.321*** (1.198–1.456)	1.283** (1.111–1.481)	1.285** (1.113–1.484)
No	1.995*** (1.872–2.126)	1.581*** (1.483–1.685)	1.604*** (1.451–1.775)	1.609*** (1.455–1.780)
Diabetes mellitus				
Yes	1.441*** (1.244–1.668)	1.360*** (1.174–1.575)	1.302* (1.048–1.618)	1.322* (1.064–1.643)
No	1.982*** (1.872–2.099)	1.517*** (1.432–1.607)	1.525*** (1.395–1.667)	1.526*** (1.396–1.668)
Hyperlipidemia				
Yes	1.499*** (1.310–1.715)	1.386*** (1.211–1.587)	1.517*** (1.231–1.869)	1.532*** (1.242–1.888)
No	1.959*** (1.849–2.076)	1.520*** (1.434–1.611)	1.486*** (1.358–1.625)	1.489*** (1.361–1.628)
Depression				
Yes	1.322** (1.094–1.598)	1.368** (1.131–1.654)	1.108 (0.848–1.448)	1.126 (0.860–1.472)
No	1.959*** (1.854–2.071)	1.501*** (1.42–1.587)	1.535*** (1.408–1.674)	1.538*** (1.411–1.678)
Anxiety				
Yes	1.249 (0.925–1.686)	1.231 (0.911–1.663)	0.998 (0.648–1.538)	0.983 (0.636–1.52)
No	1.964*** (1.861–2.073)	1.507*** (1.427–1.591)	1.510*** (1.388–1.642)	1.517*** (1.395–1.65)
Head injury				
Yes	1.137 (0.721–1.794)	0.987 (0.625–1.559)	0.989 (0.508–1.922)	0.979 (0.500–1.914)
No	1.981*** (1.878–2.09)	1.511*** (1.432–1.595)	1.502*** (1.382–1.632)	1.505*** (1.385–1.635)

Notes: 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.

Subgroup analyses (Table 4) consistently demonstrated a consistent connection between Z-drug use and an elevated risk of tinnitus, both before and after propensity score matching. Prior to matching, the adjusted HRs were 1.545 (95% CI: 1.416–1.686) for males and 1.476 (95% CI: 1.379–1.579) for females. Similar results were observed in the matched cohort, with adjusted HRs of 1.564 and 1.457, respectively. The association was most pronounced among younger individuals aged ≤39 years, with adjusted HRs of 1.989 (95% CI: 1.773–2.231) before matching and 2.009 (95% CI: 1.652–2.443) after matching, and gradually attenuated with increasing age. Across comorbidity subgroups, a general trend of elevated tinnitus risk was observed in both individuals with and without baseline conditions. In particular, sleep disorders were consistently associated with an increased risk of tinnitus (adjusted HR: 1.260; 95% CI: 1.123–1.414 before matching; 1.267; 95% CI: 1.072–1.498 after matching). However, in the subgroup of patients with chronic otitis media, depression, anxiety, or a history of head injury, no statistically significant association was observed. This lack of significance could be attributed to the fact that these conditions are major risk factors for tinnitus, potentially overshadowing or obscuring the risk associated with z-drug use.

Discussion

In this population-based cohort study, we found that the use of Z-drugs was significantly associated with an increased risk of tinnitus. After adjusting for potential confounders and applying propensity score matching, Z-drug users continued to exhibit a higher incidence of tinnitus compared to nonusers. This association remained statistically significant and was consistently observed across various demographic and clinical subgroups. To the best of our knowledge, this is the first population-based study to explore the relationship between Z-drug use and subsequent tinnitus risk.

To date, there is extremely limited research on this issue, and the relevant findings are also inconsistent. While prior studies focused on antidepressants and BZDs, our findings uniquely highlight a direct, population-based association between Z-drug use and tinnitus, expanding current understanding beyond isolated case reports. For instance, certain case reports have suggested that antidepressants, classified as CNS drugs, potentially cause hearing impairment.[17,18,25] A recent cohort study in Taiwan showed that an elevated use of different classes of antidepressants was correlated with an increased risk for sudden sensorineural hearing loss.[19] Previous studies on tinnitus have shown that the use of BZD drugs can improve tinnitus. However, there is no systematic research to support the use of Z-drugs in the treatment of tinnitus.[23] Other studies mentioned that Z-drug and tinnitus are usually indirectly related. In the studies, tinnitus in patients was related to insomnia or sleep disorders. Zopiclone (one type of z-drugs) can effectively reduce insomnia, tinnitus and ear congestion in patients with sudden hearing loss and severe insomnia.[24] As tinnitus is a symptom that often arises secondary to conditions such as hearing loss, otologic disease, or neurological dysfunction, the observed association with Z-drug use may be influenced by both pharmacologic effects and patient-related clinical characteristics.[26] Nonetheless, our findings suggest a possible association that warrants clinical attention to the potential auditory side effects of Z-drugs in susceptible populations.

Although the actual mechanism underlying the relationship between BZRA use and tinnitus risk remains unclear, it is suggested that the alteration of gamma-aminobutyric acid (GABA) plays a role in this relationship. In some previous studies, several biological mechanisms underlie the decrease in the primary inhibitory neurotransmitter, GABA, which has been implicated in auditory.[27,28] Alterations in GABA neurotransmission can disrupt the necessary inhibition that regulates spontaneous neural activity within the auditory system. The abnormal neural activity associated with tinnitus perception extends beyond the auditory system, encompassing nonauditory neural networks such as those involved in sensory, cognitive, and affective processes.[29–33] Because BZRAs target specific recognition sites in GABAAs, the primary inhibitory neurotransmitter receptor throughout the central nervous system, BZRAs may alter GABA neurotransmission and directly or indirectly affect neurotransmission, which results in tinnitus. An animal study which used large-scale RNA sequencing in aged mice to identify Gabra1 upregulation in OC/SGN, suggested that GABAA alpha1 mediated afferent inhibition may underlie ARHL. Drugs like zaleplon which target at GABAA alpha1 may have some impact on hearing function.[34] Therefore, these underlying mechanisms and reports provide explanations for the relationship between Z-drugs use and tinnitus risk. Furthermore, some reports have suggested that BZRAs cause extremely rare withdrawal symptoms. Over the past 20 years, a few studies or case reports have mentioned BZRA-related withdrawal symptoms such as sensory disturbances, especially otological side effects.[14,35–37] In this study, in alignment with earlier

research, suggests a need for heightened awareness of both BZRA-related withdrawal and its possible influence on auditory function. While these mechanisms are biologically plausible and supported by preclinical research, direct human evidence linking Z-drug use to auditory dysfunction remains limited. Our nationwide cohort findings offer complementary epidemiologic observations to earlier mechanistic insights, contributing to a more comprehensive understanding of the issue. This underscores the need for further clinical studies to validate these findings.

This study had several advantages. First, it was the first and largest sample cohort study to explore the correlation between BZRA use and subsequent tinnitus risk. Our study design enabled the identification of rare outcomes and allowed comparison with findings from previous research. Furthermore, the cohort design allowed for the evaluation of the association between BZRA use and tinnitus within a defined temporal framework. Second, our primary findings were validated through three distinct methodologies, encompassing complete cohort analyses with adjustments and a PSM model. This approach effectively mitigated confounding variables and biases, ensuring the robustness of our findings. Third, we used a stringent diagnostic criterion for our outcome measure, depending on physician-diagnosed tinnitus. Nevertheless, this study had some limitations. First, the inherent limitations of secondary administrative databases such as the NHI include the absence of important clinical information (eg, lifestyle factors, environmental exposures, over-the-counter medication use, and psychiatric symptom severity), as well as the potential for exposure misclassification. Second, information on certain ototoxic medications, including nonsteroidal anti-inflammatory drugs and salicylates, was not incorporated into our analysis, which may contribute to residual confounding. Third, the data used in this study were collected between 2001 and 2010. Although this timeframe precedes more recent datasets, Z-drugs were already widely prescribed in Taiwan during this period, and their prescribing patterns remained relatively stable Thus, the nationwide claims data still provide meaningful insights for evaluating population-level associations. Finally, as in most tinnitus-related studies, the absence of standardized objective measures for this condition remains a general challenge.[38] Future research may consider incorporating more objective or validated instruments for tinnitus assessment.

Conclusions

In conclusion, this cohort study showed that Z-drug use may be associated with an increased risk of tinnitus. These results raise important considerations regarding the potential auditory safety profile of Z-drug use. Given the observational design, however, residual confounding and misclassification cannot be fully excluded. Clinicians may consider monitoring for tinnitus symptoms in patients using Z-drugs and carefully evaluating the risk–benefit balance when prescribing these medications. Further research is needed to elucidate the underlying biological mechanisms and to replicate these findings in other settings, thereby strengthening the evidence base for clinical decision-making.

Abbreviations

aHRs, adjusted hazard ratios; CI, confidence intervals; GABA, gamma-aminobutyric acid; NHI, National Health Insurance; SDiff, standardized difference; cDDD, cumulative defined daily dose.

Data Sharing Statement

The data utilized in this study were sourced from the Taiwan Health and Welfare Data Science Center (HWDC). In accordance with national patient confidentiality regulations, these data are not publicly accessible. Interested researchers may submit applications to access the data directly to the HWDC. Application details are available at their official website: http://dep.mohw.gov.tw/DOS/np-2497-113.htm.

Ethics Approval

This study was approved by the Institutional Review Board of Tri-Service General Hospital, Taiwan (C202205001) and the requirement for informed consent was waived because the research involves secondary data that has been encrypted and de-identified.

Author Contributions

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Final approval and accountability: All authors 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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