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ARTICLE

Analysis of Drug-Related Tinnitus Based on the FDA Adverse Event Reporting System Database

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Abstract

Aims/Background Tinnitus is a very common condition, and is a side effect of many medications. The panorama of drug-induced tinnitus has widened in recent decades, and post-marketing data are needed to gain a better insight into adverse drug reactions related to tinnitus. However, there are currently few studies on drug-induced tinnitus. We aimed to explore the details of real-world drug-related tinnitus.

Methods We collected data on adverse drug reactions related to tinnitus from the Food and Drug Administration Adverse Event Reporting System (FAERS) database for the fourth quarter of 2012 to the fourth quarter of 2023. The top 25 tinnitus-associated drugs and indications were analyzed, and reporting odds ratios (RORs) were used to assess the association between drugs and adverse events (AEs).

Results A total of 29,460 patients were enrolled in our study, with a greater proportion of women (59.1%) than men (31.7%). Among all tinnitus-related drugs, duloxetine (n = 1510, ROR [95% confidence interval (CI)] = 11.99 [11.38–12.63]), ciprofloxacin (n = 938, ROR [95% CI] = 9.96 [9.33–10.63]), and adalimumab (n = 759, ROR [95% CI] = 0.68 [0.64–0.73]) displayed the strongest associations. Among all tinnitus-related indications, depression (n = 1172), rheumatoid arthritis (n = 947), and multiple sclerosis (n = 914) were the most relevant indications. Vertigo (n = 2443, ROR [95% CI] = 7.51 [7.21–7.82]), deafness (n = 1740, ROR [95% CI] = 13.50 [12.86–14.18]), and hypoacusis (n = 1550, ROR [95% CI] = 6.11 [5.81–6.43]) were the most common concomitant ototoxic AEs in patients reporting tinnitus.

Conclusion Our study mined and analyzed the AEs signals of drug-induced tinnitus and provided a reference for the safe clinical application of the drugs.

Key words: drug-induced tinnitus; adverse events; ototoxicity monitoring; Food and Drug Administration (FDA) Adverse Event Reporting System database

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Introduction

Tinnitus affects more than 740 million adults globally, with more than 120 million people reporting it as severe (Jarach et al, 2022). Severe tinnitus can cause hearing impairment, affect communication and interaction between people, affect sleep, and cause emotional problems for patients (Chen et al, 2024; Oosterloo et al, 2021). In the literature, rates of severe symptoms among tinnitus patients are between 15% and 30%. Patients reported a significant decrease in their quality of life due to tinnitus, with symptoms such as depression, anxiety disorder, difficulty concentrating, and irritability (Hall et al, 2011; Mantello et al, 2020; Pinto et al, 2010). There is a high prevalence of depressed mood and related depressive symptoms

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in patients with tinnitus, and approximately 48%–60% of chronic tinnitus sufferers are diagnosed with major depression due to long-term tinnitus-related distress (Pinto et al, 2014). These conditions place a significant burden on the global economy and society in terms of disease. However, the pathophysiological mechanism of tinnitus remains unclear. Noise, ototoxic drug use, and aging may damage the auditory system and induce tinnitus (Paciello et al, 2021; Qi et al, 2019; Zhang et al, 2020).

Drug-associated tinnitus has attracted increasing attention as an adverse drug reaction, and common drugs that can cause tinnitus include salicylic acid preparations, diuretics, and ototoxic antibiotics (Ding et al, 2016; Le et al, 2023; Sheppard et al, 2014). Signal mining based on the Spanish Pharmacovigilance System Medicinal Products for Human Use (SEFV-H) database identified 3295 adverse ototoxicity signals, of which 662 were tinnitus adverse events (AEs) signals. Eight percent of tinnitus cases were considered severe, with persistent or significant disability reported in 8.4% of cases. Full recovery occurred only in 65% of cases, making tinnitus a global, nonnegligible adverse drug reaction (Lisbona-Alquézar et al, 2020).

Ototoxic drugs, well-known to clinicians, should be avoided if possible or replaced by alternative drugs in patients carrying a gene for deafness or with a family history of deafness. Many new medications have been developed in recent years; however, the AEs that cause tinnitus have not been systematically analyzed. This adverse effect has not been included in the instructions for some medications, which can lead to chronic persistent tinnitus in patients who are unable to stop taking them in time, affecting their physical and mental health.

The Food and Drug Administration Adverse Event Reporting System (FAERS) is one of the spontaneous reporting databases currently used in the monitoring of adverse drug reactions, and the present study mined and analyzed tinnitus AEs signals due to drugs in the population to provide a reference for the safety of the clinical application of drugs.

Methods

Data Collection

We collected all available information from the FAERS database from the fourth quarter of 2012 to the fourth quarter of 2023. For consistency and accuracy, the FAERS database utilizes a standardized classification system based on the Medical Dictionary for Regulatory Activities (MedDRA) to report AEs. In our research, tinnitus was defined by the preferred term (PT) tinnitus (PT code 10043882) under the System Organ Class (SOC) category named ear and labyrinth disorders (SOC code 10013993). Only drugs classified as primary suspect (PS) of inducing tinnitus were included in this study. Duplicated cases were deleted following the recommendation of the Food and Drug Administration (FDA) by processing the Demographic (DEMO) file. The flowchart of the study is presented in **Supplementary Fig. 1**.

Signal Report

A disproportionality analysis was performed using the relative odds ratios (RORs) to detect the safety signals of the drugs. The calculation for the RORs uses a two-by-two contingency table comparing event counts for the target drug and all other drugs; the equations and criteria are listed in **Supplementary Table 1**.

Statistical Analyses

R (version 4.3.2, founded by R Development Core Team, Vienna, Australia) and RStudio (version 2023.12.0+369, founded by Posit, Boston, MA, American) were used for all the statistical analyses. Descriptive statistics for all categorical [N (%)] variables were determined for all patients' demographic and clinical characteristics and outcomes. Normality testing was performed using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Normally distributed quantitative variables were presented as mean ± SD, whereas non-normally distributed continuous variables were represented as median (interquartile range).

Results

The Demographic Characteristics of the Patients

As listed in Table 1, 29,460 patients were included in our study, with a greater proportion of women (59.1%) than men (31.7%). Most patients (31.2%) weighed between 50 and 100 kg. The majority of patients (46.4%) were aged between 18 and 64.9 years, and most adverse reactions were reported by patients (57%).

The Top 25 Drugs with Tinnitus-Related Adverse Effects and Their RORs

The top 25 drugs with tinnitus-related adverse effects are listed in Fig. 1. Patients taking duloxetine were the most likely to report adverse effects related to tinnitus, followed by ciprofloxacin and adalimumab. These drugs can be categorized into several groups according to the Anatomical Therapeutic Chemical (ATC) Index 2024. Among these groups, antidepressants and immunosuppressants were most strongly associated with tinnitus. RORs of these drugs are shown in Fig. 2. Based on the RORs, all drugs in the antidepressant, analgesic, and quinolone antibacterial categories were related to tinnitus. However, despite being the second most common group, almost all immunosuppressants were not associated with tinnitus.

The Top 25 Indications for Tinnitus-Inducing Drugs

The indications for these drugs can be classified according to the eleventh revision of the International Classification of Diseases, as illustrated in Fig. 3. Diseases of the musculoskeletal system or connective tissue rank first, followed by mental, behavioral, or neurodevelopmental disorders. In line with the medication rankings, depression had the highest incidence of drug-associated tinnitus, followed by rheumatoid arthritis, for which adalimumab, etanercept, and tofacitinib were widely used.

Table 1. Demographic characteristics of the patients.

	Overall (N = 29,460)	
	N (%)	Median (Interquartile range)
Sex		
Female	17,413 (59.1%)	
Male	9339 (31.7%)	
Missing	2708 (9.2%)	
Weight (kg)		
<50	600 (2.0%)	46.00 (5.47)
>100	1181 (4.0%)	111.00 (16.97)
50–100	9188 (31.2%)	72.00 (19.40)
Missing	18,491 (62.8%)	
Age (years)		
<18	358 (1.2%)	14.00 (5.00)
>85	261 (0.9%)	88.00 (11.00)
18–64.9	13,671 (46.4%)	50.00 (18.00)
65–85	4790 (16.3%)	71.00 (8.00)
Missing	10,380 (35.2%)	
Reporter		
Customer	16,787 (57.0%)	
Health professional	2047 (6.9%)	
Lawyer	511 (1.7%)	
Physician	4722 (16.0%)	
Pharmacist	1555 (5.3%)	
Register nurse	13 (0.0%)	
Other	2603 (8.8%)	
Missing	1222 (4.1%)	

Onset Time of Tinnitus

The time of induction of tinnitus was recorded in 5046 (17.13%) patients. The time from taking the drug to tinnitus onset is presented in Fig. 4. The period with the greatest number of patients was 0–5 days (n = 1522), followed by 31–180 days (n = 1053). Remarkably, 167 (3.31%) patients experienced tinnitus after taking the drug for more than 1800 days.

Concomitant Ototoxic Reactions in Patients with Drug-Induced Tinnitus

In addition to tinnitus, patients developed other ototoxic reactions, as listed in Fig. 5. According to RORs, patients suffering from tinnitus also have an increased risk of all events with a PT number of cases greater than 2. Vertigo (n = 2443, ROR [95% confidence interval (CI)] = 7.51 [7.21–7.82]), deafness (n = 1740, ROR [95% CI] = 13.50 [12.86–14.18]), and hypoacusis (n = 1550, ROR [95% CI] = 6.11 [5.81–6.43]) were the most common concomitant ototoxic AEs in patients reporting tinnitus.

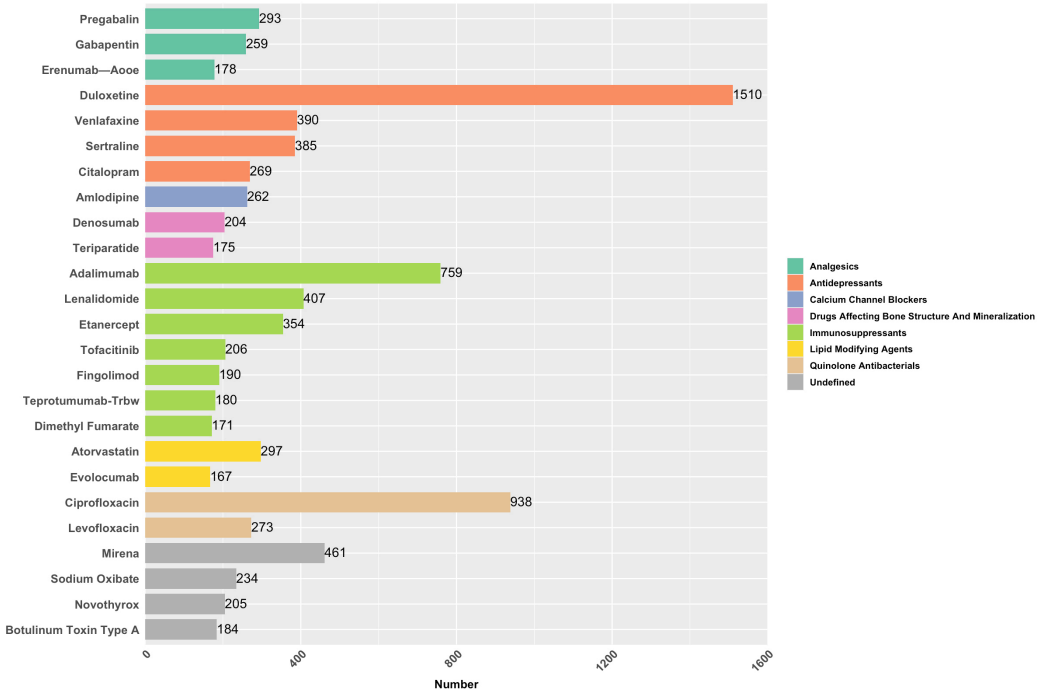


Fig. 1. Top 25 tinnitus-inducing drugs and associated preferred term (PT) numbers. These drugs were categorized into eight groups according to the Anatomical Therapeutic Chemical (ATC), of which antidepressants (n = 2554), immunosuppressants (n = 2267), and quinolone antibacterial agents (n = 1211) were the most common drugs associated with tinnitus. Among the individual drugs, duloxetine (n = 1510), ciprofloxacin (n = 938), and adalimumab (n = 759) were the three most relevant drugs.

Discussion

Tinnitus is a common clinical manifestation of otogenic damage and has been documented as a side effect of many medications. However, there is a lack of studies summarizing drug-associated tinnitus, and there are only a few case reports of tinnitus induced by medications such as baclofen and benzodiazepines (Auffret et al, 2014; Laskey and Opitz, 2020). To the best of our knowledge, this is the largest real-world study on drug-induced tinnitus.

We found a higher prevalence of drug-induced tinnitus in women compared to men, which is consistent with the findings of Lisbona-Alquézar et al (2020). However, a published epidemiological study revealed a greater prevalence of tinnitus in males than in females (Wu et al, 2015). On the other hand, a Spanish epidemiological study revealed that tinnitus was more prevalent in women (Arnold et al, 2022). These findings suggest that the gender-specific features of tinnitus may vary according to the population. With respect to patient age, we found that the adult group was more affected by tinnitus than the other groups, according to the FAERS database. This could be explained by the greater use of ototoxic drugs, such as antineoplastics or antibiotics, in adult patients.

Antidepressants are well-known for causing tinnitus (Clewes, 2012). We found that duloxetine was associated with tinnitus in the greatest number of patients in FAERS. This drug is mainly used for treating depression and pain, and the drug's

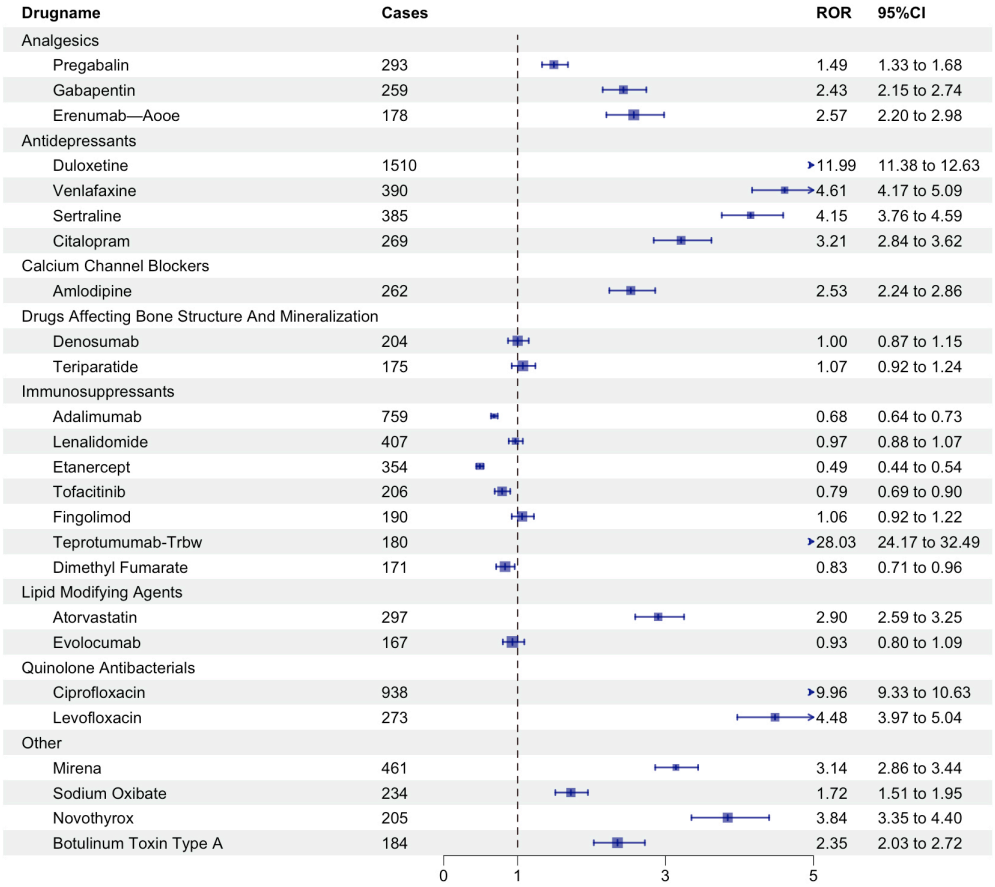


Fig. 2. The reporting odds ratios (RORs) of the top 25 drugs. All drugs in the antidepressant, analgesic, and quinolone antibacterial categories were related to tinnitus, while almost all immunosuppressants were not associated with tinnitus.

label indicates that some patients may experience withdrawal symptoms such as tinnitus and dizziness after discontinuing the drug after long-term use. Cases of tinnitus have also been reported in depressed patients after the use of venlafaxine (Ahmad, 1995; Pondrom and Brahm, 2009). 5-hydroxytryptamine (5-HT), also known as serotonin, plays an important role in the pathogenesis of tinnitus, and selective serotonin reuptake inhibitors, such as duloxetine and sertraline, have been reported to induce tinnitus by disturbing serotonin metabolism. There is a strong relationship between tinnitus and depression and anxiety, with tinnitus patients being at increased risk (Chen et al, 2024). When patients on these drugs experience severe tinnitus that interferes with mood and sleep, it is recommended that they undergo a professional assessment of their condition. Quinolones and aminoglycosides are among the most common ototoxic drugs (Rivetti et al, 2023). We found that ciprofloxacin topped the list of antibacterial agents with AEs including tinnitus, which may be related to clinicians' preference for using this drug class for treating urinary tract and respiratory tract infections (Refaeian et al, 2023). Conversely, aminoglycosides are not on the list because clinicians less commonly use them due to their association with ototoxicity. Etanercept and lenalidomide are common immunosuppressive agents, and adverse reactions reported in the FAERS, including tinnitus, are common.

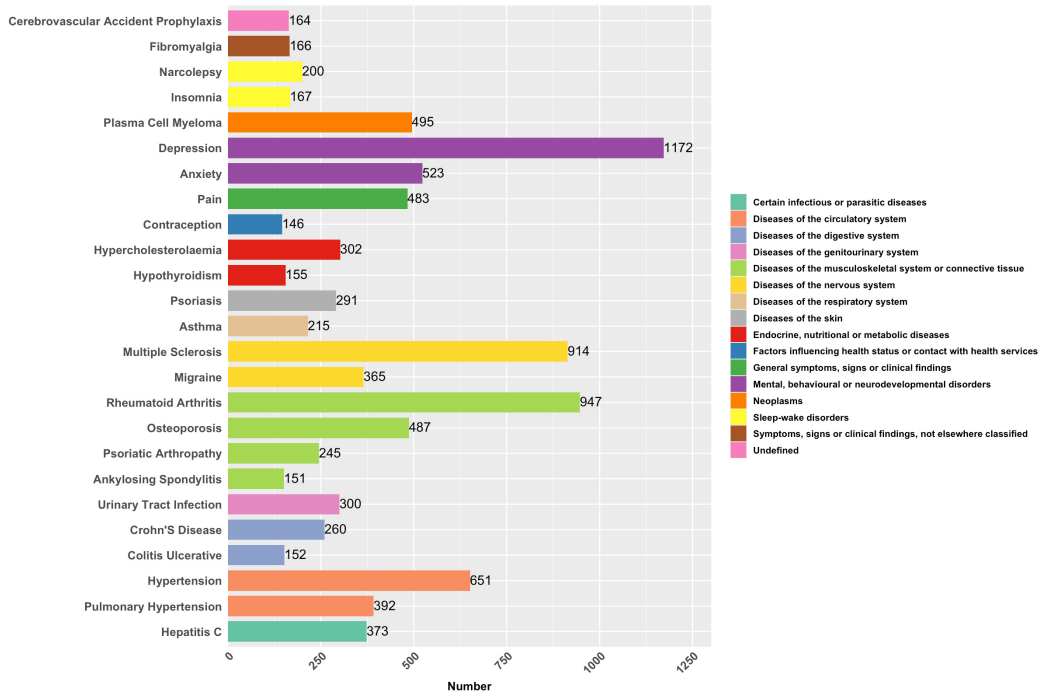


Fig. 3. Top 25 indications for tinnitus-inducing drugs. The top 25 indications were categorized into 16 groups according to the eleventh revision of the International Classification of Diseases, with 'diseases of the musculoskeletal system or connective tissue' (n = 1830), 'mental, behavioral or neurodevelopmental disorders' (n = 1695), and 'diseases of the nervous system' (n = 1279) being the most common. For a single indication, depression (n = 1172), rheumatoid arthritis (n = 947), and multiple sclerosis (n = 914) were the most relevant disorders for tinnitus-related drugs.

Our study revealed a strong correlation between Mirena use and tinnitus, and the use of Mirena may lead to an imbalance in the ratio of estrogen and progesterone in the body, inducing tinnitus symptoms (Ding et al, 2016). However, tinnitus is not mentioned as a side effect in the instructions. The main component of Mirena is levonorgestrel, which is an antiestrogenic progestogen. Some research has shown that an imbalance in the ratio between estrogen and progesterone can lead to morphological and physiological damage to the cochlea (Bittar et al, 2001). We found that tinnitus can also be caused by the use of amlodipine, which acts as a calcium channel antagonist and may affect the blood supply to the inner ear, leading to tinnitus. Diuretics are also commonly used antihypertensive agents, have been shown to cause unique pathological changes in the cochlea, thereby causing symptoms such as tinnitus and hearing loss (Altissimi et al, 2020; Ding et al, 2016).

During the database search for drug-associated tinnitus over the last 10 years, ototoxicity-associated drugs, including aminoglycosides, cisplatin, and salicylic acid agents, were notably absent from the top 25. In contrast, serotonin-inhibiting antidepressants and quinolones demonstrated strong AEs signals. Barbieri et al (2019)'s review of the Italian Medicines Agency database of ototoxic adverse drug reactions from 2001 to 2017 revealed that the drugs most likely to cause ototoxicity were aminoglycoside and quinolone antibiotics, followed by antineoplastic and cardiovascular drugs. Conversely, in the SEFV-H systematic review, quinolones and antidepressants showed strong AEs signals for ototoxic adverse effects (Lisbona-

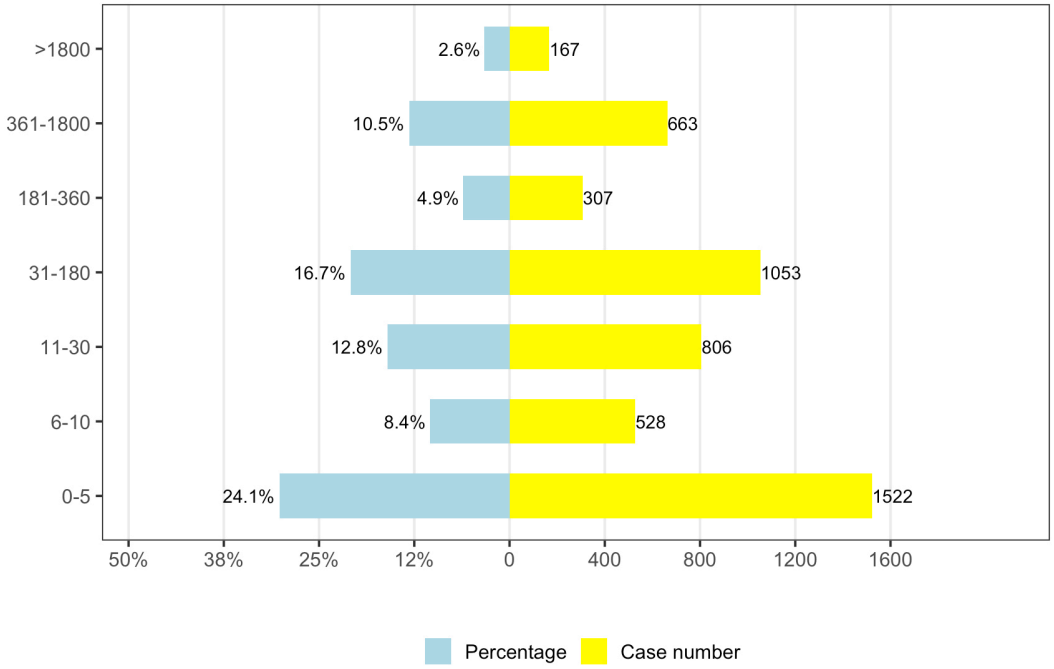
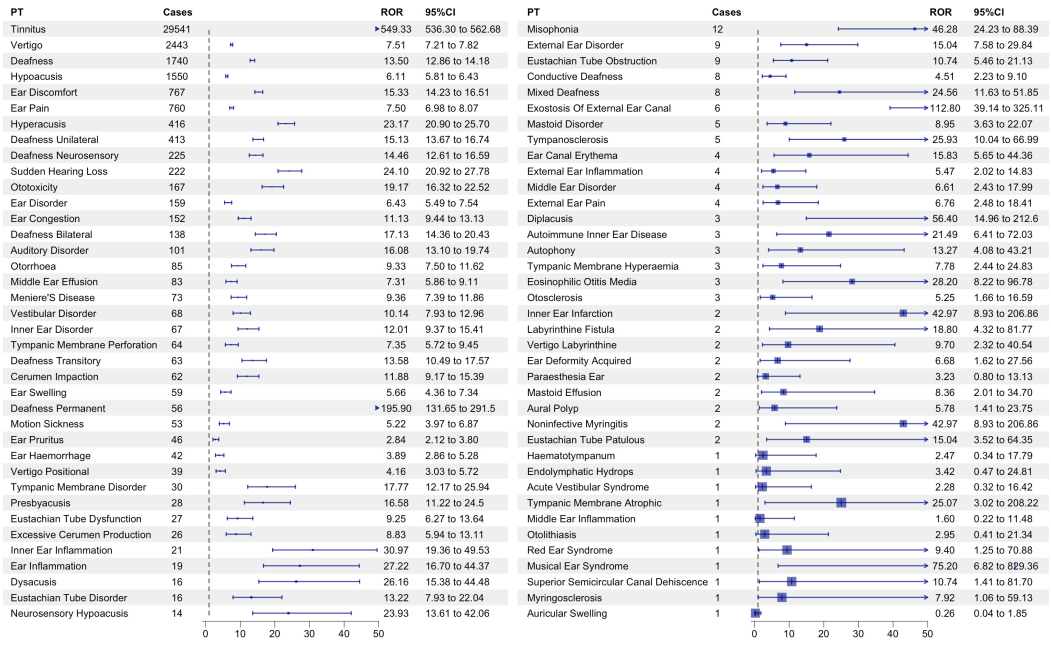


Fig. 4. The time to tinnitus onset distribution. Most patients (n = 1522) developed tinnitus within five days of taking the primary suspected drug. However, 167 patients experienced tinnitus after taking the drug for more than 1800 days.



PT	Cases	ROR	95%CI
Tinnitus	29541	549.33	536.30 to 562.68
Vertigo	2443	7.51	7.21 to 7.82
Deafness	1740	13.50	12.86 to 14.18
Hypoacusis	1550	6.11	5.81 to 6.43
Ear Discomfort	767	15.33	14.23 to 16.51
Ear Pain	760	7.50	6.98 to 8.07
Hyperacusis	416	23.17	20.90 to 25.70
Deafness Unilateral	413	15.13	13.67 to 16.74
Deafness Neurosensory	225	14.46	12.61 to 16.59
Sudden Hearing Loss	222	24.10	20.92 to 27.78
Ototoxicity	167	19.17	16.32 to 22.52
Ear Disorder	159	6.43	5.49 to 7.54
Ear Congestion	152	11.13	9.44 to 13.13
Deafness Bilateral	138	17.13	14.36 to 20.43
Auditory Disorder	101	16.08	13.10 to 19.74
Otorrhoea	85	9.33	7.50 to 11.62
Middle Ear Effusion	83	7.31	5.86 to 9.11
Meniere'S Disease	73	9.36	7.39 to 11.86
Vestibular Disorder	68	10.14	7.93 to 12.96
Inner Ear Disorder	67	12.01	9.37 to 15.41
Tympanic Membrane Perforation	64	7.35	5.72 to 9.45
Deafness Transitory	63	13.58	10.49 to 17.57
Cerumen Impaction	62	11.88	9.17 to 15.39
Ear Swelling	59	5.66	4.36 to 7.34
Deafness Permanent	56	195.90	131.65 to 291.5
Motion Sickness	53	5.22	3.97 to 6.87
Ear Pruritus	46	2.84	2.12 to 3.80
Ear Haemorrhage	42	3.89	2.86 to 5.28
Vertigo Positional	39	4.16	3.03 to 5.72
Tympanic Membrane Disorder	30	17.77	12.17 to 25.94
Presbyacusis	28	16.58	11.22 to 24.5
Eustachian Tube Dysfunction	27	9.25	6.27 to 13.64
Excessive Cerumen Production	26	8.83	5.94 to 13.11
Inner Ear Inflammation	21	30.97	19.36 to 49.53
Ear Inflammation	19	27.22	16.70 to 44.37
Dysacusis	16	26.16	15.38 to 44.48
Eustachian Tube Disorder	16	13.22	7.93 to 22.04
Neurosensory Hypoacusis	14	23.93	13.61 to 42.06

PT	Cases	ROR	95%CI
Misophonia	12	46.28	24.23 to 88.39
External Ear Disorder	9	15.04	7.58 to 29.84
Eustachian Tube Obstruction	9	10.74	5.46 to 21.13
Conductive Deafness	8	4.51	2.23 to 9.10
Mixed Deafness	8	24.56	11.63 to 51.85
Exostosis Of External Ear Canal	6	112.80	39.14 to 325.11
Mastoid Disorder	5	8.95	3.63 to 22.07
Tympanosclerosis	5	25.93	10.04 to 66.99
Ear Canal Erythema	4	15.83	5.65 to 44.36
External Ear Inflammation	4	5.47	2.02 to 14.83
Middle Ear Disorder	4	6.61	2.43 to 17.99
External Ear Pain	4	6.76	2.48 to 18.41
Diplacusis	3	56.40	14.96 to 212.6
Autoimmune Inner Ear Disease	3	21.49	6.41 to 72.03
Autophony	3	13.27	4.08 to 43.21
Tympanic Membrane Hyperaemia	3	7.78	2.44 to 24.83
Eosinophilic Otitis Media	3	28.20	8.22 to 96.78
Otosclerosis	3	5.25	1.66 to 16.59
Inner Ear Infarction	2	42.97	8.93 to 206.86
Labyrinthine Fistula	2	18.80	4.32 to 81.77
Vertigo Labyrinthine	2	9.70	2.32 to 40.54
Ear Deformity Acquired	2	6.68	1.62 to 27.56
Paraesthesia Ear	2	3.23	0.80 to 13.13
Mastoid Effusion	2	8.36	2.01 to 34.70
Aural Polyp	2	5.78	1.41 to 23.75
Noninfective Myringitis	2	42.97	8.93 to 206.86
Eustachian Tube Patulous	2	15.04	3.52 to 64.35
Haematotympanum	1	2.47	0.34 to 17.79
Endolymphatic Hydrops	1	3.42	0.47 to 24.81
Acute Vestibular Syndrome	1	2.28	0.32 to 16.42
Tympanic Membrane Atrophic	1	25.07	3.02 to 208.22
Middle Ear Inflammation	1	1.60	0.22 to 11.48
Otolithiasis	1	2.95	0.41 to 21.34
Red Ear Syndrome	1	9.40	1.25 to 70.88
Musical Ear Syndrome	1	75.20	6.82 to 829.36
Superior Semicircular Canal Dehiscence	1	10.74	1.41 to 81.70
Myringosclerosis	1	7.92	1.06 to 59.13
Auricular Swelling	1	0.26	0.04 to 1.85

Fig. 5. The RORs of concomitant ototoxic reactions. Based on the RORs, PTs with more than three cases were all clinically significant.

Alquézar et al, 2020). This finding is consistent with our analysis of tinnitus AEs signals. In our study, we found that the most common comorbid ototoxic symptoms of tinnitus were vertigo, deafness, and hearing loss. Clinically, pure-tone air (PTA) is useful adjunct for ototoxicity monitoring (Robler et al, 2022). The diagnosis of

ototoxicity is based on patient's history and audiological evaluation with PTA. In patients receiving long-term therapy with tinnitus-related drugs, it is recommended to perform PTA every three to six months even after the end of the treatment. To assess hearing loss, additional tests such as otoacoustic emissions, vocal audiometry, auditory brainstem response, and vestibular examinations should be performed (Ganesan et al, 2018; Lanvers-Kaminsky et al, 2017; Lord, 2019; Robler et al, 2022). Vestibular examination can detect vestibular function, especially in patients with tinnitus combined with vertigo. The Tinnitus Handicap Inventory (THI) and Tinnitus Functional Index (TFI) are widely used and validated tinnitus questionnaires (Polanski et al, 2016) and have also been used in several clinical trials assessing tinnitus alleviation. When using tinnitus-associated medications, clinicians recommend that patients undergo the above tests to detect cochlear and vestibular damage early to avoid irreversible ototoxicity. Mental health problems associated with tinnitus should also be addressed, and timely intervention by a psychologist should be sought.

We acknowledge the limitations and strengths of our study. The main strength is that we conducted the first overview of all drug-induced tinnitus cases from the FAERS database. Our shortcomings are as follows: (1) The AEs in the database are spontaneously reported by a variety of entities, including medical institutions, health insurance agencies, pharmaceutical companies, civil affairs departments, patients, attorneys, and other members of the community, and the FDA does not require that the reporters provide the causal relationship between the reported AEs and the drugs; moreover, because various types of people have different reporting standards, the descriptions of the content of the reports vary to some extent, which may lead to inaccuracies and incompleteness. This may have resulted in inaccurate and incomplete reports. (2) The database is for the USA population, which may display different patterns of racial diversity compared with other populations. (3) We have found a number of medications that can cause tinnitus, but due to space limitations, we have only listed the top 25 medications and the top 25 indications.

Conclusion

Our data reveal that the use of serotonin reuptake inhibitor antidepressants, quinolones, painkillers, amlodipine, calcium channel antagonists, and drugs for treating symptoms of proptosis in patients with hyperthyroidism, such as teprtumumab-trbw, atorvastatin, menzies, sodium oxybate, novothyrox, and botulinum toxin type A, is strongly correlated with the occurrence of tinnitus. Pharmacological tinnitus is more common in women than in men, and tinnitus is most often combined with symptoms of vertigo and deafness. Physicians should be aware of the clinical significance of tinnitus and its consequences for patient's quality of life, and they should be conscious of the importance of reporting these cases to health authorities.

Key Points

- Women are more susceptible to drug-induced tinnitus than men.
- Drug-induced tinnitus is common, especially in those patients on antidepressants and quinolone antibacterial agents.
- Patients with drug-induced tinnitus should be watched for other ototoxic reactions.
- In patients receiving long-term therapy with tinnitus-related drugs, ototoxicity monitoring is necessary.

Availability of Data and Materials

The data and materials used in this study can be available from the corresponding author upon reasonable request.

Author Contributions

LW, YT and PZ designed the research. LW and YT performed the research. PZ provided help and advice on the data collecting. LW analyzed the data. LW wrote the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0380.

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