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MAIN ARTICLE

The use of benzodiazepines for tinnitus: systematic review

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Abstract

Objectives: To investigate the effectiveness of benzodiazepine use for subjective tinnitus and to consider this in the context of the concomitant side effects.

Methods: A systematic search of several databases using the terms 'tinnitus' and 'benzodiazepines' was conducted to find clinical trials of benzodiazepines and comparators in tinnitus patients. These studies were then assessed for risk of bias.

Results: Six clinical trials were included. Clonazepam was found to be effective in three studies, but these studies had limitations regarding adequate blinding. The effectiveness of alprazolam was equivocal. Diazepam was not effective in two studies and oxazepam was effective in one study.

Conclusion: Benzodiazepine use for subjective tinnitus does not have a robust evidence base. Clonazepam has the most evidence to support its use and is relatively less likely to lead to abuse because of its longer half-life, but caution is still needed given the other serious side effects.

Key words: Benzodiazepines; Tinnitus; Review

Introduction

Tinnitus is defined as the perception of a sound without an external acoustic source, often described as a perception of ringing, whistling or buzzing in one or both ears.[1] Tinnitus affects up to 30 per cent of the adult population, with 6 per cent of these individuals reporting incapacitating symptoms.[2] It is important to distinguish between objective tinnitus, which can be generated from vascular, musculoskeletal or respiratory sources, and subjective tinnitus which has a neurophysiological origin.[1] Chronic subjective tinnitus is difficult to treat. The aim for most patients who do not achieve symptom resolution is to manage the symptom by tolerating the sensation and minimising its impact on everyday life.[3]

It has been hypothesised that tinnitus perception may arise, in part, from increases in spontaneous neural activity in the central auditory system.[4] Benzodiazepines potentiate the inhibition caused by the release of γ-aminobutyric acid (GABA). Hence, if tinnitus is due to auditory central nervous system hyperactivity, then it is likely that benzodiazepines lessen tinnitus symptoms by reducing this hyperactivity through enhancing GABA-mediated inhibition.[5] Benzodiazepines are frequently suggested as one of the medication classes for the management of tinnitus, in addition to anticonvulsant agents and anti-depressant medications.[6,7]

However, benzodiazepines have a significant side-effect profile and, critically, a potential for misuse and abuse. Benzodiazepines contributed to 49 per cent of the total number of drug-related deaths investigated by the Coroners Court of Victoria (Australia) in 2010.[8] Benzodiazepines were also the second most common drug involved in ambulance attendances in Victoria, after alcohol, in 2012–2013.[9] In fact, alprazolam was recently up-scheduled from a schedule 4 (prescription only) to a schedule 8 (drug of dependence) drug category by the Australian Therapeutic Goods Administration, in February 2014. This was partly a result of the recognition of its increased morbidity and mortality in overdoses, the evidence of widespread misuse, and the greater diversion from licit sources to illicit use and abuse.[10]

With such high stakes, it was surprising that no previous systematic review had been conducted to assess the sum of evidence for benzodiazepine use in tinnitus cases. This systematic review aimed to determine the strength of the evidence for benzodiazepine use in tinnitus management and to weigh that against the risks associated with their use, in order to inform future practice.

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Materials and methods

This systematic review was registered with Prospero (an international database of prospectively registered systematic reviews) with the registration number CRD42014010772. The databases included in the search, conducted in June 2014, were the Cochrane Library, PubMed, Embase, Web of Science and PsycInfo. The Medical Subject Heading terms used were 'tinnitus' and 'benzodiazepines' for all databases. The PubMed database had the clinical trial filter applied. All databases were searched using the full historical range. Only articles published in the English language were included. The study design did not necessarily need to be a clinical trial. The population targeted were human subjects reported as suffering from tinnitus; there were no exclusions regarding the method of tinnitus diagnosis. The intervention was required to be a benzodiazepine medication, used for any duration. Interventions included the following specific agents, which are available in Australia: alprazolam, bromazepam, clobazam, clonazepam, diazepam, flunitrazepam, lorazepam, midazolam, nitrazepam and oxazepam.[11] For the comparison, it was necessary that at least one other non-benzodiazepine intervention was employed as part of the treatment or that a placebo was used. There were no exclusions based on outcome measures.

The process of article identification and assessment for eligibility is described in Figure 1.[12] One investigator completed the screening of the records; however, both investigators reviewed all full text articles independently and discussed any discrepancies until consensus was reached. The assessment of risk of bias of the studies was assessed according to the Cochrane Collaboration tool.[13] This assessment and the data extraction were again conducted by both investigators independently, with subsequent discussion regarding any discrepancies.

Results

There were six studies eligible for inclusion (Figure 1).[5,14–18] All of these studies were randomised trials of at least one benzodiazepine versus a placebo or versus another non-benzodiazepine comparator. An overview of the study designs is shown in Table I.

All studies were assessed for risk of bias; the results are summarised in Table II. At an outcome level, one of the most important domains of risk of bias was blinding of the participants, because of the fact that the outcome measures for tinnitus all contain a degree of subjectivity.[13] Three studies reported that the participants were blinded, but did not provide a clear description of this process.[5,14,15] The cross-over design was a feature in four studies,[5,15–17] with two studies not specifying the 'wash-out' period (when no active medication was received).[15,16] At a study level, the investigations with the least risk of bias across all domains were those by Jalali *et al.*[17] and Johnson *et al.*[18] At a review level, the overall level of bias is unclear as most of the information is from studies at a low or unclear risk of bias across domains.[13]

The results of the six included studies are shown in Table III. Clonazepam was shown to be effective in treating tinnitus in all three studies in which it was investigated.[5,14,15] The two alprazolam studies showed opposing results.[17,18] Diazepam was shown to not be effective in both studies that investigated it.[15,16] Lastly, oxazepam was shown to be effective in the one trial that investigated it.[15]

Discussion

This systematic review found six clinical trials of benzodiazepines used in the treatment of tinnitus; these studies employed a number of different agents, with variable results. The results of these trials need to be interpreted in the context of a number of limitations and risks of bias in the study designs.

Tinnitus is a subjective hearing sensation, and as such it is difficult to accurately measure and thereby assess therapeutic results.[19] The studies in this review used audiometry, visual analogue scales, the Tinnitus Handicap Inventory, tinnitus loudness assessments and a unspecified self-rating tool to measure the tinnitus sensation of participants. Tinnitus loudness assessments generally involve the participant matching reported tinnitus to externally presented sounds.[20] This method is highly dependent on the participant's intellectual capacity and concentration, and the experience of the assessor.[19] In addition, it has been demonstrated that tinnitus loudness does not correlate well with the impact of tinnitus on the participant;[21] this limits the clinical relevance of this outcome measure. Visual analogue scales are simple to use, which is advantageous. However, the results can be variable; psychosomatic factors in particular can significantly affect tinnitus perception.[16,19] The Tinnitus Handicap Inventory has been found to be a valid instrument for use in tinnitus intervention studies.[22] However, there may be problems associated with floor effects; this was suggested as a possible reason for the negative results in one of the included alprazolam trials.[17]

Given the subjective nature of tinnitus, a subjective outcome measure will remain a limitation in future studies until such a time when advances in neuroimaging and electrophysiological methods may provide objective measurements.[23] However, a consensus on a tinnitus outcome measure that could reliably measure the impact on quality of life of tinnitus and fluctuations in severity would facilitate co-operation between research centres and allow more meaningful evaluations and comparison of outcomes.[23]

The reliance on subjective measures for tinnitus assessment highlighted the weakness in many of the studies included in this review. Given the subjective nature of the assessment, it was critical that the participants were blinded to their allocation, and this aspect was not always clearly outlined in the reported

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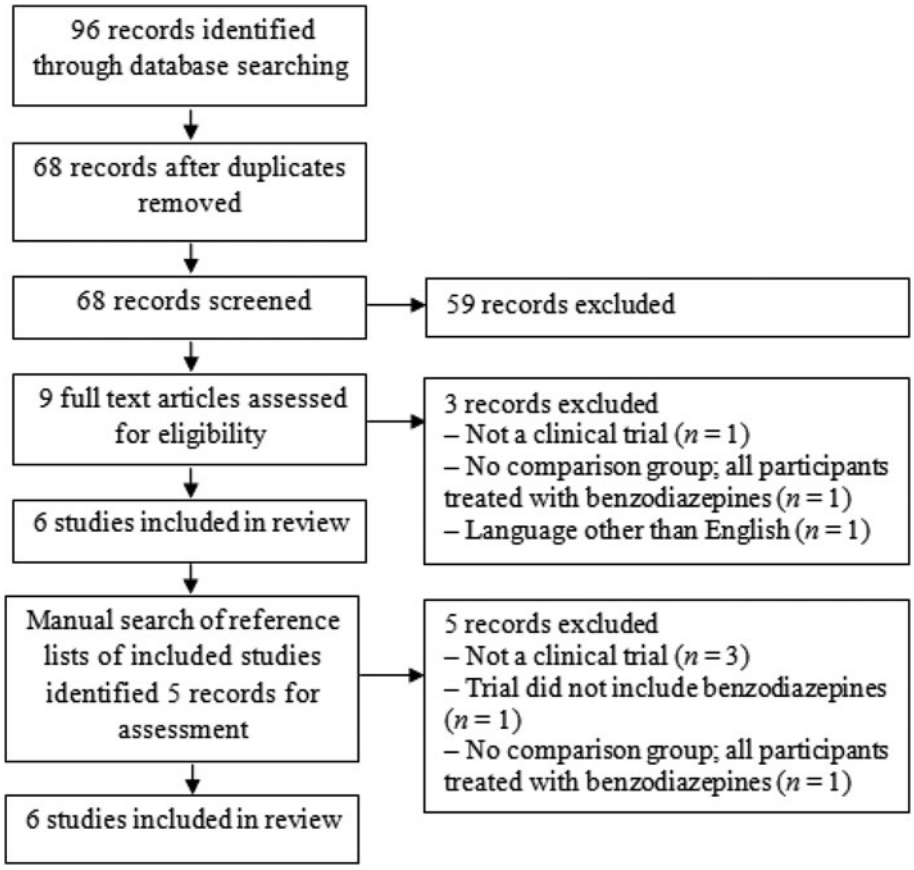

FIG. 1
Results of literature search presented as a Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') flow chart.

methods of the studies. If these studies were inadequate in achieving blinding, then the likely direction of this performance bias is an overestimation of effect.[13] Successful blinding was achieved by some studies that used comparators with similar side-effect profiles and no cross-over design, which demonstrates that a superior methodology is possible for future studies.

The cross-over designs may have biased results in subsequent trials, as the participants could have feasibly compared their experience with the previous agent(s) and this might have influenced their perception and experience of their tinnitus. Han *et al*. presented a cross-over design study where both possible orders of the medications were studied in order to avoid this issue, and the advantage of participants acting as their own controls was retained (thus eliminating the potential for variability in a design associated with a separate control group).[5]

The treatment regimes in all of the reviewed studies were of short duration, lasting from 4 to 12 weeks. This significantly limits the evidence for benzodiazepine use in cases of chronic subjective tinnitus, which can last for years. This was demonstrated by a temporal population-based study conducted in Australia, where tinnitus persisted after five years in over three-quarters of the cohort.[24] In the study by Johnson *et al*., which had the longest treatment duration, the authors concluded that benzodiazepines are not appropriate as a long-term measure. Nevertheless, after the conclusion of the trial, some patients experienced tinnitus relief for several weeks before the tinnitus returned to its original level. Furthermore, some patients were able to continue taking the drug at low doses after the trial. However, this data were not presented in the paper. More long-term studies are required to assess the effectiveness of all benzodiazepines as a long-term strategy for this chronic condition.

Benzodiazepines carry a risk of iatrogenic dependence, and have a considerable list of side effects including: sedation or drowsiness (38–75 per cent), memory impairment (up to 15 per cent), unsteadiness, slurring of speech, irritability, mood changes, aggression and reduced motivation.[25] Benzodiazepine use is also associated with a significant increase in the risk of traffic accidents.[26] The prescription of benzodiazepines should be based on a comprehensive assessment of the patient that identifies a specific diagnostic reason or target symptoms for which good evidence exists for benzodiazepine efficacy.[27] Further caution is needed because of the large inter-subject variability in the pharmacokinetics of benzodiazepines,[5] which requires individualisation of therapy and slow titration of dosage.

Clonazepam was the benzodiazepine identified in this review with the greatest evidence base for its use

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TABLE I
STUDIES INCLUDED IN REVIEW

Study	Year	Location	Design	Participants	Intervention	Comparator(s)	Outcome measures	Follow-up period
Kay[16]	1981	Liverpool, UK	Prospective, double-blind, triple cross-over comparison	21 participants with tinnitus. Exclusions: history of cardiovascular problems	Diazepam 4–6 mg	Mexiletine 400–600 mg, betahistine 16–24 mg & placebo	VAS	Variable. 1 mth per medication trial; only 11 participants fully completed all trials
Lechtenberg & Shulman[15]	1984	New York, USA	Prospective, randomised, single-blind comparison	116 participants, aged 18–85 y, suffering from subjective tinnitus for at least 1 mth	Diazepam DNS, oxazepam 10–50 mg & clonazepam 0.5–3 mg	Meclizine 12.5–25 mg, chlorpheniramine 8–12 mg, dexchlorpheniramine 2–8 mg, carbamazepine up to 600 mg & no treatment	Patient assessment of tinnitus volume & location, sleep & activity impairment (using 1–5 scale)	Variable. 1 mth per medication trial
Johnson *et al.*[18]	1993	Portland, USA	Prospective, randomised, double-blind, placebo-controlled trial	40 participants, aged 21–65 y, with constant (non-fluctuant) tinnitus for >1 y	Alprazolam 0.5–1.5 mg	Placebo (lactose)	Audiometry, tinnitus loudness assessment, VAS	12 wk
Bahmad *et al.*[14]	2006	Brasilia, Brazil	Prospective, randomised, single-blind, placebo-controlled trial	36 participants with severe tinnitus (defined by VAS score >7) for at least 6 months, with an otological diagnosis. Exclusions: tinnitus secondary to surgery, chronic otitis media, contraindication to trial medication	Clonazepam 0.5–2 mg	Clonazepam (0.5–2 mg) with gabapentin (300–900 mg), & placebo	VAS	6 wk
Jalali *et al.*[17]	2009	Rasht, Iran	Prospective, randomised, triple-blind, cross-over, placebo-controlled trial	36 participants, aged 21–65 y, with non-pulsatile tinnitus for >1 y. Exclusions: Ménière's disease, vestibular schwannoma, otosclerosis, temporal lobe tumour, depression, anxiety, hearing aid use, alprazolam intolerance	Alprazolam 0.5–1.5 mg	Placebo (chlorpheniramine maleate 4–12 mg)	Tinnitus loudness assessment, VAS, THI	9 wk per medication trial + 1 wk wash-out = 19 wk
Han *et al.*[5]	2012	Chuncheon, Korea	Prospective, randomised, open-label, cross-over comparison	38 participants, aged 16–80 y, with tinnitus for >2 mth. Exclusions: sedating or anti-depressant medications, tinnitus with curable cause, contraindication to trial medication, pregnancy, mental retardation, psychosis, severe cognitive disorders	Clonazepam 0.5–2 mg	Ginkgo biloba 40–160 mg	Audiometry, tinnitus loudness & pitch assessment, VAS, THI	3 wk per medication trial + 2 wk wash-out = 8 wk

VAS = visual analogue scale; mth = months; y = years; wk = weeks; THI = Tinnitus Handicap Inventory; DNS = dose not specified

TABLE II
ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Study (year)	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of assessment outcome	Incomplete outcome data	Selective reporting	Other bias
Kay[16] (1981)	Unclear. 'Randomised allocation schedule'	Unclear. Not enough is known about randomisation pattern	Low risk. Allocation was made by pharmacy; pharmacy did not directly dispense medication, which was identical in appearance & dosage regimen	Low risk. Participants were blinded to intervention, so unlikely to bias self-rating; however, outcome measure was subjective	High risk. 10 participants (48%) did not complete full cycle, & participants who only completed part of a 28-day trial were included in results	High risk. Only initial month of results presented despite 3 medication trials of 28 days planned for each participant	Cross-over design introduces potential for bias because of order that medication was given, especially as trial was stopped before all cycles were completed for some participants
Lechtenberg & Shulman[15] (1984)	Unclear. 'Randomly allocated'	High risk. Sequence was generated 'according to the order in which they entered the study', which is likely to have been predictable	High risk. Personnel were not blinded. Participants who took active treatment were blinded, but not those who received no treatment	Low risk. Participants were blinded to intervention, so unlikely to bias self-rating; however, outcome measure was subjective	Unclear. Trial had no defined length & participants were unaware they were participating in a trial	Low risk. All outcome measure results reported for all medication trials, & distribution of trial enrolments presented	Cross-over design introduces potential for bias because of order that medication was given, & potential for carry-over effects of previous medication
Johnson *et al.*[18] (1993)	Unclear. 'Randomly assigned'	Unclear. Not enough is known about randomisation pattern	Low risk. Allocation was made by author who was uninvolved with outcome assessment. Medication was identical in dosage regimen	Low risk. Participants were blinded to intervention, so unlikely to bias self-rating; only 1 outcome measure was subjective	Low risk. 36 participants (90%) completed programme	Low risk. All outcome measure results & reported side effects presented	
Bahmad *et al.*[14] (2006)	Unclear. 'Randomly assigned'	Unclear. Not enough is known about randomisation pattern	High risk. Personnel were not blinded. No description of participant blinding was provided	Unclear. If participants were blinded to intervention, this is unlikely to bias self-rating outcome measure; however, measure was subjective	Low risk. 30 participants (83%) completed programme	Low risk. All outcome measure results presented	Participants had an otological diagnosis & tinnitus of predominantly cochlear origin, which is different to populations in other included studies
Jalali *et al.*[17] (2009)	Low risk. Randomisation by fixed block randomisation into 2 groups	Low risk. Sequence generated was difficult to predict	Low risk. Allocation was known to pharmacy; pharmacy dispensed medication into envelopes with study subject numbers. Medications were similar in appearance & side effects, & had same dosage regimen	Low risk. Participants were blinded to intervention, so unlikely to bias self-rating; however, outcome measures were subjective	Low risk. 14 participants in group 1 (78%) & 16 in group 2 (89%) completed trial. All 30 participants were included in analysis	Low risk. All outcome measure results presented	Cross-over design introduces potential for bias because of order that medication was given. However, as wash-out period was 1 week, carry-over bias is unlikely

Han *et al.*[5] (2012)	Low risk. Randomisation using digital random number generator	Low risk. Sequence generated was difficult to predict	High risk. Personnel were not blinded. Study described as open-label trial, but participants were reported to be 'blind to their [medication's] identities'. No further description was given	Unclear. If participants were blinded to intervention, this is unlikely to bias self-rating outcome measures; however, some outcome measures were subjective	Low risk. High but balanced attrition rates of 46% (16 out of 35) in clonazepam group & 37% (11 out of 30) in ginkgo biloba group	Low risk. All outcome measure results presented	Cross-over design introduces potential for bias because of order that medication was given; however, this is counteracted by both possible orders of medications being presented & analysed. Given that wash-out period was 2 weeks, a carry-over bias is also unlikely

in managing tinnitus. Despite the fact that all three studies supported the use of clonazepam, none had adequate reporting of participant blinding, which may have led to overestimation of the results. Interestingly, one of the studies only included participants with a known otological cause of tinnitus (the other studies required participants simply to have the tinnitus symptom);[14] thus, the population in that study was slightly different to that in the other studies. Nevertheless, all three studies yielded positive results.

Clonazepam is a long-acting benzodiazepine with a plasma half-life of 20–40 hours.[28] This longer half-life reduces the potential for abuse, as shorter half-life drugs have greater dependence potential.[29] However, it can lead to accumulation when given repeatedly, and undesirable effects may manifest only after several days or weeks, particularly in those with hepatic or renal impairment.[28]

The evidence to support the use of alprazolam in tinnitus was conflicting, with both studies involved having low risk of bias. It is possible that the difference in results is related to potentially different rates of depression or anxiety in the two study groups. The study with the negative result specifically excluded patients who scored positively on the Beck Depression Inventory and Hamilton Rating Scale for Anxiety (with cut-off points of 16 and 14 respectively), or who were diagnosed with a psychiatric disorder in a structured clinical interview conducted by a psychiatrist.[17] The study with positive results did not have this exclusion criteria, although the Beck Depression Inventory was used in the initial assessment.[18] The reported results were that only two participants had scores suggestive of mild mood disturbance and all other participants had scores within normal limits.[18] It is difficult to compare these two studies with this limited information; however, if the participants in the negative results study had lower rates of depression and anxiety, it is feasible that this partly accounts for the discrepancy in the two studies' results.

Alprazolam is a shorter acting benzodiazepine, with a plasma half-life of 12–15 hours.[28] A number of studies have reported that people find it difficult to withdraw from alprazolam, with most suggesting that up to half of the recipients are unable to discontinue use within a month.[25] In addition, alprazolam causes other adverse reactions including aggression and mood changes, with 10 per cent in one trial becoming hostile while being treated with alprazolam.[25]

Oxazepam was investigated in only one study. This study had multiple identified risks of bias, particularly regarding the cross-over design and lack of blinding, which limits the reliability of the evidence supporting its use in tinnitus cases.[15] Oxazepam has a shorter plasma half-life of 6–20 hours;[28] however, it does not have the same abuse potential as alprazolam because of its more gradual action onset, which limits the sensation of intoxication immediately after ingestion.[30]

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TABLE III
SUMMARY OF OUTCOMES IN INCLUDED STUDIES

Study (year)	Benzodiazepine	Result	Outcome measure	Conclusion
Kay[16] (1981)	Diazepam	No significant difference between other drugs & placebo	VAS	Diazepam, along with other medications trialled, did not appear effective in tinnitus management, but results were inconclusive
Lechtenberg & Shulman[15] (1984)	Diazepam	1 participant out of 15 showed (<50%) improvement	Patient assessment of tinnitus (rating scale)	Both oxazepam & clonazepam were highly effective, & exhibited statistically significant efficacy over anti-histamines & carbamazepine. Diazepam caused no significant change in tinnitus
	Oxazepam	12 participants out of 23 showed improvement (4 with <50%, 1 with 50–80% & 7 with >80%)		
	Clonazepam	18 participants out of 26 showed improvement (6 with <50%, 8 with 50–80% & 4 with >80%)		
Johnson *et al.*[18] (1993)	Alprazolam	No change in hearing thresholds or speech discrimination scores overall	Audiometry	Alprazolam provides therapeutic relief for some patients with tinnitus
		Significant reduction in subjective loudness at end of weeks 4 & 12. No statistically significant changes in placebo group	VAS	
		Significant reduction in subjective loudness at end of weeks 4 & 12. No statistically significant changes in placebo group	Tinnitus loudness	
Bahmad *et al.*[14] (2006)	Clonazepam	Statistically significant decrease in tinnitus intensity & annoyance compared with placebo, but no difference when compared with clonazepam plus gabapentin	VAS	Clonazepam reduces tinnitus annoyance & intensity when compared with placebo, but there is no difference when combined with gabapentin
	Clonazepam & gabapentin	Statistically significant decrease in tinnitus intensity & annoyance compared with placebo, but no difference when compared with clonazepam alone		
Jalali *et al.*[17] (2009)	Alprazolam	No significant difference overall, but significantly greater improvement with alprazolam *vs* placebo on catastrophic subscale	THI	Insufficient evidence to support overall superiority of alprazolam *vs* placebo
		Significantly greater improvement in alprazolam group	VAS	
		No statistically significant difference	Tinnitus loudness	
Han *et al.*[5] (2012)	Clonazepam (2 groups: clonazepam then ginkgo biloba & ginkgo biloba then clonazepam)	Statistically significant reduction in mean THI scores from beginning to end of both clonazepam trials	THI	Clonazepam is effective in treating tinnitus
		Statistically significant reduction in VAS scores for loudness, annoyance & awareness from beginning to end of both clonazepam trials	VAS	
		Statistically significant reduction in matched tinnitus loudness but not for median pitch from beginning to end of both clonazepam trials	Tinnitus loudness	

VAS = visual analogue scale; THI = Tinnitus Handicap Inventory

Diazepam, with a long half-life of 25–50 hours,[28] was found to be ineffective in treating tinnitus in both studies where it was investigated. However, this result must be considered in the context of the limitations of the studies, particularly the study by Kay which was not completed because of the effects of another drug in the trial.[16]

There have been several experimental studies that support the reduction of hyperactivity in the central auditory cortex by GABA-mediated agents. Using single-photon emission computed tomography and the benzodiazepine radioligand ^{123}I-iomazenil, it has been shown that there are diminished benzodiazepine binding sites in the medial temporal lobe cortex of patients with tinnitus of a predominantly central origin.[31] Receptor binding studies in animal models of tinnitus using long-term salicylate treatment also suggest a decrease in the number of $GABA_A$ receptor binding sites in the inferior colliculus.[32]

However, there remains the possibility that the effect of benzodiazepines is due to a general anxiolytic effect rather than a direct effect on the neurophysiological cause of tinnitus,[33] or due to a reduction in neuronal activity by a mechanism not involved in the generation of tinnitus.[34] It is well known that co-morbid mental disorders, particularly depression and anxiety, are very common in patients with tinnitus.[35] Indeed, in this review, the study by Jalali *et al*. was the only one that excluded participants with depression or anxiety, and it yielded a negative result.[17]

- **Chronic subjective tinnitus is difficult to treat; most affected patients should aim for symptom control**
- **Benzodiazepines have a significant side-effect profile, and potential for abuse and dependence**
- **Benzodiazepine use for tinnitus does not have a robust evidence base; more long-term trials with less risk of performance bias are needed**
- **Clonazepam has the most evidence to support its use; it has a long half-life which reduces the potential for abuse, but consideration of other side effects is needed**
- **Alprazolam has equivocal evidence and a significant side-effect profile; strong consideration of another benzodiazepine or class of drug is recommended**

This systematic review excluded clinical trials that did not utilise a non-benzodiazepine comparator. This was considered necessary in order to ensure that the evidence collected on the effectiveness of benzodiazepines in tinnitus was as robust as possible. This criterion led to two studies in particular being excluded during the full text review process.[36,37] Interestingly, both of these studies examined the effectiveness of clonazepam in tinnitus: one examined clonazepam in combination with gabapentin[37] and the other (a large retrospective review) examined patients who took clonazepam alone.[36] Both studies supported the use of clonazepam in tinnitus, which adds further weight to the findings of this systematic review.

Conclusion

Overall, benzodiazepine use in the medical management of subjective tinnitus does not have a robust evidence base. Longer-term trials with less risk of performance bias are needed. Clonazepam has the most evidence to support its use and is relatively less likely to lead to abuse because of its longer half-life, but caution is still needed given the other serious side effects. Diazepam has no evidence to support its use, and alprazolam, which has high abuse potential, has equivocal evidence.

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