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Betahistine for tinnitus (Protocol)

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[Intervention Protocol]

Betahistine for tinnitus

Deborah A Hall[1], Inge Wegner[2], Adriana Leni Smit[2], Don McFerran[3], Inge Stegeman[2]

[1]NIHR Nottingham Biomedical Research Centre, Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham, UK. [2]Department of Otorhinolaryngology & Head and Neck Surgery, University Medical Center Utrecht, Utrecht, Netherlands. [3]ENT Department, Essex County Hospital, Colchester Hospital University NHS Foundation Trust, Colchester, UK

Contact address: Deborah A Hall, NIHR Nottingham Biomedical Research Centre, Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Ropewalk House, 113 The Ropewalk, Nottingham, NG1 5DU, UK. deborah.hall@nottingham.ac.uk.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of betahistine in patients with subjective idiopathic tinnitus.

BACKGROUND

This is a new protocol for a new Cochrane Review. The 'Description of the condition' and 'Diagnosis and clinical management of tinnitus' sections are based on the Cochrane Review 'Amplification with hearing aids for patients with tinnitus and co-existing hearing loss' (Hoare 2014). Other sections are based on the Cochrane protocol 'Betahistine for Ménière's disease or syndrome' (van Esch 2018). They are both reproduced with permission.

Tinnitus is defined as the perception of sound in the absence of an external source (Jastreboff 2004). It is typically described by those who experience it as a ringing, hissing, buzzing or whooshing sound and is thought to result from abnormal neural activity at some point or points in the auditory pathway, which is erroneously interpreted by the brain as sound. Tinnitus can be either objective or subjective. Objective tinnitus refers to the perception of sound that can also be heard by the examiner and is usually due to turbulent blood flow or muscular contraction (Roberts 2010). Most commonly, however, tinnitus is subjective; the sound is only heard by the person experiencing it and no source of the sound is identified (Jastreboff 1988).

Tinnitus affects between 5% and 43% of the general population and prevalence increases with age (McCormack 2016). It can be experienced acutely, recovering spontaneously within minutes to weeks, but is considered chronic and unlikely to resolve spontaneously when experienced for more than three months (Gallus 2015; Hall 2011).

For many people, tinnitus is persistent and troublesome, and has disabling effects such as insomnia, difficulty concentrating, difficulties in communication and social interaction, and negative emotional responses such as anxiety and depression (Hall 2018). In approximately 90% of cases chronic subjective tinnitus is comorbid with some degree of hearing loss, which may confound these disabling effects (Fowler 1944; Sanchez 2002). Nevertheless, the association between hearing loss and tinnitus is not simple or straightforward; not all people with hearing loss experience tinnitus, and conversely some people with clinically normal hearing

have tinnitus (Baguley 2013). It has been reported that 40% of patients are unable to identify what health condition is associated with their tinnitus onset, i.e. the tinnitus is idiopathic (Henry 2005).

Description of the condition

Diagnosis and clinical management of tinnitus

There is no standard procedure for the diagnosis or management of tinnitus. Practice guidelines and the approaches described in studies of usual clinical practice typically reflect differences between the clinical specialities of the authors or differences in the clinical specialities charged with meeting tinnitus patients' needs (medical, audiology/hearing therapy, clinical psychology, psychiatry), or the available resources of a particular country or region (access to clinicians or devices, for example) (Biesinger 2011; Cima 2012; Department of Health 2009; Hall 2011; Henry 2008; Hoare 2011). Common across current clinical guidelines for the assessment of subjective tinnitus (Fuller 2017), is a recommendation for the use of written questionnaires to assess tinnitus and its impact on patients by measuring tinnitus symptom severity (e.g. impact of tinnitus on quality of life, activities of daily living or sleep), and a judgement about patients who are experiencing a degree of psychological distress (including depression or anxiety).

Clinical management strategies include education and advice, relaxation therapy, tinnitus retraining therapy (TRT), cognitive behavioural therapy (CBT), sound enrichment using ear-level sound generators or hearing aids, and drug therapies to manage co-morbid symptoms such as sleep difficulties, anxiety or depression (for example, Department of Health 2009; Tunkel 2014). As yet, no drug has been approved for tinnitus by a regulatory body (e.g. the European Medicines Agency or US Food and Drug Administration).

Pathophysiology

Many people with chronic tinnitus have some degree of measurable hearing loss (Ratnayake 2009), and the prevalence of tinnitus increases with greater hearing loss (Han 2009; Martines 2010). The varying theories of tinnitus generation involve changes in either function or activity of the peripheral (cochlea and auditory nerve) or central auditory nervous systems (Henry 2005). Theories involving the peripheral systems include the discordant damage theory, which predicts that the loss of outer hair cell function, where inner hair cell function is left intact, leads to a release from inhibition of inner hair cells and aberrant activity (typically hyperactivity) in the auditory nerve (Jastreboff 1990). Such aberrant auditory nerve activity can also have a biochemical basis, resulting from excitotoxicity or stress-induced enhancement of inner hair cell glutamate release with upregulation of N-methyl-D-aspartate (NMDA) receptors (Guitton 2003; Sahley 2001).

In the central auditory system, structures implicated as possible sites of tinnitus generation include the dorsal cochlear nucleus (Middleton 2011; Pilati 2012), the inferior colliculus (Dong 2010; Mulders 2010), and the auditory and non-auditory cortex (discussed further below). There is a strong rationale that tinnitus is a direct consequence of maladaptive neuroplastic responses to hearing loss (Moller 2000; Mühlnickel 1998). This process is triggered by sensory deafferentation and a release from lateral inhibition in the central auditory system allowing irregular spontaneous hyperactivity within the central neuronal networks involved in sound processing (Eggermont 2004; Rauschecker 1999; Seki 2003). As a consequence of this hyperactivity, a further physiological change noted in tinnitus patients is increased spontaneous synchronous activity occurring at the subcortical and cortical level, measurable using electroencephalography (EEG) or magnetoencephalography (MEG) (Dietrich 2001; Tass 2012; Weisz 2005). Another physiological change thought to be involved in tinnitus generation is a process of functional reorganisation, which amounts to a change in the response properties of neurons within the primary auditory cortex to external sounds. This effect is well demonstrated physiologically in animal models of hearing loss (Engineer 2011; Noreña 2005). Evidence in humans, however, is limited to behavioural evidence of cortical reorganisation after hearing loss, demonstrating improved frequency discrimination ability at the audiometric edge (Kluk 2006; McDermott 1998; Moore 2009; Thai-Van 2002; Thai-Van 2003), although Buss 1998 did not find this effect. For comprehensive reviews of these physiological models, see Adjamian 2009 and Noreña 2011.

It is also proposed that spontaneous hyperactivity could cause an increase in sensitivity or 'gain' at the level of the cortex, whereby neural sensitivity adapts to the reduced sensory inputs, in effect stabilising mean firing and neural coding efficiency (Noreña 2011; Schaette 2006; Schaette 2011). Such adaptive changes would be achieved at the cost of amplifying 'neural noise' due to the overall increase in sensitivity, ultimately resulting in the generation of tinnitus.

Increasingly, non-auditory areas of the brain, particularly areas associated with emotional processing, are also implicated in bothersome tinnitus (Rauschecker 2010; Vanneste 2012). Vanneste 2012 describes tinnitus as "an emergent property of multiple parallel dynamically changing and partially overlapping sub-networks", implicating the involvement of many structures of the brain more associated with memory and emotional processing in tinnitus generation. However, identification of the structural components of individual neural networks responsible for either tinnitus generation or tinnitus intrusiveness, which are independent of those for hearing loss, remains open to future research (Melcher 2013).

One further complication in understanding the pathophysiology of tinnitus is that not all people with hearing loss have tinnitus and not all people with tinnitus have a clinically significant and

measurable hearing loss. Other variables, such as the profile of a person's hearing loss, may account for differences in their tinnitus report. For example, König 2006 found that the maximum slope within audiograms was higher in people with tinnitus than in people with hearing loss who do not have tinnitus, despite the 'non-tinnitus' group having the greater mean hearing loss. This suggests that a contrast in sensory inputs between regions of normal and elevated threshold may be more likely to result in tinnitus. However, this finding is not consistent across the literature (Sereda 2011; Sereda 2015).

Description of the intervention

First registered in 1968, betahistine is an oral drug that, by 2006, was estimated to have been prescribed to more than 130 million people worldwide (Jeck-Thole 2006). The indication for taking betahistine is to treat patients with Ménière's disease (Electronic Medicines Compendium 2015). However, many patients are given betahistine off-licence to treat idiopathic subjective tinnitus (Hall 2011; McFerran 2018) and vertigo (Murdin 2016), even when these symptoms are not associated with Ménière's disease. The recommended daily dose of betahistine is 24 mg to 48 mg per day divided into two or three single doses containing 8 mg, 16 mg or 24 mg (Jeck-Thole 2006). Although gastrointestinal side effects are cited in many formularies, the rate of adverse effects in patients taking betahistine is not significantly different from those taking placebo in comparison studies (Murdin 2016).
Betahistine hydrochloride (or dihydrochloride) is a derivative of betahistine. Alternative formulations of betahistine include betahistine mesylate (or mesilate), dimesylate and maleate.

How the intervention might work

Betahistine is a weak histamine H1 receptor agonist and a potent histamine H3 receptor antagonist. One postulated mechanism of action of the drug is reduction of endolymphatic pressure through improved microvascular circulation in the stria vascularis of the cochlea (Martinez 1972). In addition, inhibition of activity in the vestibular nuclei may contribute to rebalancing neural activity and expedite the recovery process (Lacour 2007; Timmerman 1994). Studies have shown that betahistine reaches a peak plasma concentration in about one hour and it has a plasma half-life of approximately 3.5 hours (Electronic Medicines Compendium 2015). The maximal vestibular therapeutic effect will last approximately three to four hours (Electronic Medicines Compendium 2015).
For Ménière's disease/syndrome these pharmacological characteristics are thought to reduce the intensity and duration of vertigo symptoms in the short term (under three months) and additionally prevent attacks in the longer term (over three months). For tinnitus, betahistine is thought to work by improving blood flow to certain areas within the inner ear. However, it is not fully understand how betahistine actually interacts within the inner ear to reduce tinnitus symptoms. In some countries, prescription behaviour differs according to whether tinnitus is acute (< 3 months) or chronic (≥ 3 months) (Hall 2011). This may reflect a belief that duration of tinnitus is a modifier of treatment success.

Why it is important to do this review

In England alone there are an estimated ¾ million GP consultations every year where the primary complaint is tinnitus (El-Shunnar 2011), equating to a major burden on healthcare services. A study reported over 100,000 prescriptions for betahistine being filled every month in England (Phillips 2008), and nearly 10% of general practitioners prescribe betahistine for tinnitus. There is a published Cochrane Review of betahistine for Ménière's disease (idiopathic) or Ménière's syndrome (secondary to established inner ear disorders) (James 2001), and a new protocol for an update (van Esch 2018). Both examine tinnitus as a secondary outcome. However, there is no existing Cochrane Review of betahistine for tinnitus as a primary outcome, without the comorbidities of vertigo and hearing loss. Assessment of the effect of betahistine in the treatment of subjective idiopathic tinnitus is therefore warranted.

OBJECTIVES

To assess the effects of betahistine in patients with subjective idiopathic tinnitus.

METHODS

Criteria for considering studies for this review

Types of studies

We will **include** studies with the following design characteristics:

- randomised controlled trials, including cluster-randomised (cross-over trials will be eligible if data from before the cross-over are extractable, to avoid the potential for a carry-over phenomenon).

We will **exclude** studies with the following design characteristics:

- quasi-randomised controlled studies.

We will apply no restrictions on language, year of publication or publication status.

Types of participants

Patients of any age with acute or chronic subjective idiopathic tinnitus. Participants who have received betahistine previously will be eligible for inclusion.

Types of interventions

Betahistine: any dose regimens or formulations and for any duration of treatment.
The comparators are placebo, no intervention or education and information only.
The main comparison will be:

- betahistine *versus* placebo.

Other possible comparison pairs include:

- betahistine *versus* no intervention; or
- betahistine *versus* education and information only.

Concurrent use of other medication or other treatment will be acceptable if used equally in each group. For example, betahistine with an additional intervention versus placebo with an identical additional intervention. Where an additional intervention was used equally in both groups, we will analyse this as a separate comparison.

Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies.

Primary outcomes

- Tinnitus loudness (a change in subjective perception) measured using either patient-reported instruments (including visual analogue scales or numerical rating scales) or performance-based procedures (including Tinnitus Loudness Matching or Minimum Masking Level).
- Significant adverse effects: upper gastrointestinal discomfort.

Secondary outcomes

- Tinnitus symptom severity (such as the impact of tinnitus on quality of life, activities of daily living and sleep), as measured by the global score on a multi-item tinnitus questionnaire (Table 1). These include:
    - Tinnitus Functional Index (Meikle 2012);
    - Tinnitus Handicap Inventory (Newman 1996);
    - Tinnitus Handicap Questionnaire (Kuk 1990);
    - Tinnitus Reaction Questionnaire (Wilson 1991);
    - Tinnitus Questionnaire (Hallam 2009; Hiller 2006); and
    - Tinnitus Severity Scale (Sweetow 1990).
- Depressive symptoms or depression as measured by a validated instrument including the Beck Depression Inventory (Beck 1988; Beck 1996), the depression scale of the Hospital Anxiety and Depression Scale (HADS; Zigmond 1983), or the Hamilton Rating Scale for Depression (Hamilton 1960).
- Anxiety symptoms or generalised anxiety as measured by a validated instrument including the Beck Anxiety Inventory (Beck 1988a), the anxiety scale of the HADS (Zigmond 1983), or the Anxiety Sensitivity Index (Reiss 1986).
- Health-related quality of life as measured by any appropriate scale including the Short-Form health survey (Hays 1993), WHOQOL-BREF (Skevington 2004), other WHOQOL versions and the Health Utilities Index (Furlong 2001).
- Other adverse effects; headache, allergic skin reactions (pruritis, rashes) and exacerbation of tinnitus.

In addition, we will report the new core outcome for trials of pharmacological interventions for tinnitus, this being **tinnitus intrusiveness** (Fackrell 2017). As there is not yet an agreed definition of this concept, intrusiveness will be measured by a single item patient-reported visual analogue scale or numerical rating scale. Based on the pharmacological properties of the drug described above, we will assess outcomes as short-term (less than three months) and long-term (three to six months). We will also consider whether these outcomes are sustained beyond six months.

Search methods for identification of studies

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- the Cochrane ENT Register (search to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL, via the Cochrane Register of Studies (CRS) to date);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to date);
- Ovid Embase (1974 to date);
- LILACS (Latin American and Caribbean Health Science Information database; 1982 to date);
- Web of Knowledge, Web of Science (1945 to date);
- ClinicalTrials.gov, www.clinicaltrials.gov (search via the Cochrane Register of Studies to date);

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to date).

The subject strategies for databases will be modelled on the search strategy designed for CENTRAL (Appendix 1). Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011)).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. The Information Specialist will also run non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

We will not perform a separate search for adverse effects of betahistine for tinnitus. We will consider adverse effects described in the included studies only.

Data collection and analysis

Selection of studies

Three authors (DAH, DM and IS) will independently scan the initial search results to identify studies that appear to meet the inclusion criteria. The authors will then review the full-text articles of the retrieved studies and apply the inclusion criteria independently. We will resolve any differences in opinion about which studies to include in the review by discussion or, failing that, by consultation with one of the other authors (IW, DS).

Data extraction and management

Three authors (DAH, IW and DS) will independently extract data from the studies using a purposefully designed data form. We will extract data so as to allow an intention-to-treat analysis. We will pilot the data extraction form on a subset of articles and revise it as indicated before formal data extraction begins. Where necessary or where insufficient data are provided for the study, we will contact the authors for further information.

Information to be extracted will include: trial design, country of recruitment, setting, funding, conflict of interest (any author), methods or randomisation and blinding, power, number of participants, inclusion and exclusion criteria, type of intervention and control(s), total dose per day (mg), method of administration, concomitant treatment, treatment duration, treatment fidelity, type and duration of follow-up, definition of outcomes and endpoints, and statistical tests.

Data to be extracted will include: baseline characteristics of participants (age, sex, duration of tinnitus, tinnitus symptom severity, tinnitus loudness estimates, details of co-morbid hearing loss, anxiety or depression), and details of any attrition or exclusion.

Outcome data to be extracted will include: group mean and standard deviation at pre- and post-intervention and follow-up, and results of any statistical tests of between-group comparisons.

With regard to subgroup analysis, we will extract data to allow grading according to duration of tinnitus and treatment protocol (dose and duration of drug treatment). If betahistine doses differ among the intervention groups within a study, we will extract data on the highest dose and compare this to placebo. Extraction of data on co-morbidity will involve, for example, depressive symptoms, generalised anxiety and reduced sound level tolerance).

We will also contact authors where further information is required that is not contained within the trial publication or in an accessible database. If not reported or provided by the authors we will estimate standard deviations in RevMan 5.3 (RevMan 2014) using the available data, such as standard errors, confidence intervals, P values and t values. Where data are only available in graph form, authors will make and agree numeric estimates.

After independent data extraction, all authors will review the extracted data for disagreements, and revisit and discuss the relevant studies as required to reach a final consensus.

Assessment of risk of bias in included studies

Two authors (IW and IS) will undertake assessment of the risk of bias of the included trials independently, with the following taken into consideration, as guided by the*Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias (e.g. lack of an intervention control as a comparator, improper statistical analysis).

We will use the Cochrane 'Risk of bias' tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias. We will resolve differences of opinion by discussion. If no consensus is reached, we will consult the other authors.

Measures of treatment effect

The primary outcome in this review will be the change in tinnitus loudness, which is likely to be a continuous variable. For intervention effect measures using continuous data, we plan to calculate

the mean difference (MD) between groups with a 95% confidence interval (CI), provided that the selected studies used the same scale of measurement. If different scales having been used, we plan to calculate the standardised mean difference (SMD) (Cohen's d effect size (ES)). A positive effect size indicates that the treatment group achieved better outcomes than the control group.
We will analyse dichotomous data as risk ratios (RR) with 95% CIs.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-RCTs with the cluster as the unit of analysis. For more recent studies, it is most likely that clusters have been taken into account in the analyses. If not, we will adjust for the clusters using the methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Cross-over trials

For subjective idiopathic tinnitus, it is unlikely that symptom severity returns to its baseline level after the first treatment period. Therefore, we will only use data from cross-over trials if data from before the cross-over can be obtained.

Multi-arm studies

In the event that we find studies with more than two groups (e.g. two or more active treatments being tested against placebo), we will establish which of the comparisons are relevant to the systematic review and relevant to each of the meta-analyses that we may implement. As we anticipate that participants will have been included in several groups, there is a risk of unit of analysis error. As a result, we will ensure that participants are included only once per meta-analysis. Where the study design used independent groups, we will treat the study as an independent comparison.

Repeated observations on participants

The unit of analysis will be the participant. If studies evaluate the effect over a longer time period, we may record the results at multiple time points. To avoid unit of analysis error when combining study results in a single meta-analysis (and therefore counting the same participants in more than one comparison), we will define different outcomes related to the periods of follow-up and we will perform separate analyses.

Dealing with missing data

Where necessary and where sufficient data from the study are not provided, we will contact the authors of the study requesting further details about missing data and reasons for the incompleteness of the data. If no useful response is obtained, we will impute data if we judge the data to be 'missing at random'. If we judge data to be 'missing not at random', the missing data may affect the overall results; we will therefore not impute data. In the latter case, we will conduct sensitivity analysis with different assumptions.
We will be alert to potential mislabelling or non-identification of standard errors and standard deviations. Our methods for imputation will be according to chapter 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).
If data are missing, we will use available case analysis using all data (as reported) for all randomised patients available at the end of the study/time point of interest, regardless of the actual treatment received. We will consider the quality of outcome assessment as a study limitation (GRADE) and not as a stratifying factor.

Assessment of heterogeneity

We will determine whether the selected studies suffer from clinical, statistical and methodological heterogeneity. We will quantify statistical heterogeneity using the I^2 statistic and the Chi^2 test. With respect to the I^2 statistic, an approximate guide to interpretation is provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). If the I^2 value is 50% or higher, the data can be considered to suffer from substantial or considerable heterogeneity. For the Chi^2 test, we will use the indicator that where the Chi^2 is greater than the degrees of freedom (where the degrees of freedom are the number of studies K minus 1), then heterogeneity is likely to be present. We will consider heterogeneity to be statistically significant if the P value is less than 0.10. Subsequently, we will perform the meta-analysis using fixed-effect (in the absence of heterogeneity) and random-effects modelling (in the presence of heterogeneity). If the level of heterogeneity remains unclear we will seek statistical advice.

Assessment of reporting biases

We will search for and request study protocols for the included studies and, where available, we will evaluate whether there is evidence of selective reporting. If a meta-analysis contains at least 10 studies, we will assess publication bias using a funnel plot and Egger's test.

Data synthesis

If more than one study is identified for a given option, and if combining studies is appropriate, we will use RevMan 5.3 to perform meta-analyses (RevMan 2014). We will pool data from RCTs using a fixed-effect model, except when heterogeneity is found. We will pool continuous data using the SMD measure, if more than one instrument is used to measure the same outcome.
We will consider the psychometric properties of the outcome instruments with regard to their suitability for pooling. For meta-analyses of the primary outcome (tinnitus loudness), whenever studies report outcomes measured by more than one instrument, data will be included only when those instruments are known to measure the same underlying construct of tinnitus loudness (high convergent validity) and show a similar direction of treatment-related effect. We will take the same approach for secondary outcomes.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will carry out subgroup analyses. This will be restricted to a very small number of subgroups and we will perform a significance test for interaction with the treatment effect. We will clearly specify the boundaries for defining inclusion and exclusion in advance, and for age we will consider whether specifying a cut-off of 16 or 18 years has an effect on the findings. The planned subgroups are defined by:

- age (children < 16 or 18 years and adults ≥ 16 or 18 years);
- duration of tinnitus (acute ≤ 3 months and chronic > 3 months);
- dose of betahistine administered (minimum daily dose of 8 mg to a maximum of 148 mg);
- additional interventions (betahistine with and without an additional intervention).

Sensitivity analysis

We will conduct a sensitivity analysis by excluding those studies with a high risk of bias, thereby checking the robustness of the conclusion from the studies included in the meta-analysis. In addition, we will use sensitivity analyses for studies in which data were imputed.

GRADE and 'Summary of findings' table

Two independent authors (IW and IS) will use the GRADE approach to rate the overall quality of evidence using GRADEpro GDT (https://gradepro.org/). The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We will include a 'Summary of findings' table, constructed according to the recommendations described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), for the following comparison(s):

- betahistine *versus* placebo;
- betahistine *versus* no intervention; and
- betahistine *versus* education and information only.

We will include the following outcomes in the 'Summary of findings' table:

- tinnitus loudness;
- significant adverse events (tinnitus exacerbation);
- tinnitus symptom severity;
- other adverse effects (upper gastrointestinal discomfort, headache and allergic skin reactions);
- depressive symptoms; and
- symptoms of generalised anxiety.

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Samantha Cox, Cochrane Information Specialist, designed the search strategy for the review.

REFERENCES

Additional references

Adjamian 2009
Adjamian P, Sereda M, Hall DA. The mechanisms of tinnitus: perspectives from human functional neuroimaging. *Hearing Research* 2009;**253**(1-2):15–31. [PUBMED: 19364527]

Baguley 2013
Baguley D, McFerran D, Hall D. Tinnitus. *Lancet* 2013; **382**(9904):1600–7. [PUBMED: 23827090]

Beck 1988
Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. *Clinical Psychology Review* 1988;**8**(1):77–100. DOI: https://doi.org/10.1016/0272-7358(88)90050-5

Beck 1988a
Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology* 1988;**56**(6): 893–7. [PUBMED: 3204199]

Beck 1996
Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. San Antonio, Texas: Psychological Corporation, 1996.

Biesinger 2011
Biesinger E, Del Bo L, De Ridder D, Goodey R, Herraiz C, Kleinjung T, et al. Algorithm for the diagnostic & therapeutic management of tinnitus. http://www.tinnitusresearch.org/images/files/migrated/TRI_Tinnitus_Flowchart.pdf (accessed 21 May 2018) 2011.

Buss 1998
Buss E, Hall JW 3rd, Grose JH, Hatch DR. Perceptual consequences of peripheral hearing loss: do edge effects exist for abrupt cochlear lesions?. *Hearing Research* 1998; **125**(1-2):98–108. [PUBMED: 9833964]

Cima 2012
Cima RF, Maes IH, Joore MA, Scheyen DJ, El Refaie A, Baguley DM, et al. Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial. *Lancet* 2012;**379**(9830): 1951–9. [PUBMED: 22633033]

Department of Health 2009
Department of Health. *Provision of Services for Adults with Tinnitus. A Good Practice Guide*. London: Central Office of Information, 2009.

Dietrich 2001
Dietrich V, Nieschalk M, Stoll W, Rajan R, Pantev C. Cortical reorganization in patients with high frequency cochlear hearing loss. *Hearing Research* 2001;**158**(1-2): 95–101. [PUBMED: 11506941]

Dong 2010
Dong S, Rodger J, Mulders WH, Robertson D. Tonotopic changes in GABA receptor expression in guinea pig inferior colliculus after partial unilateral hearing loss. *Brain Research* 2010;**1342**:24–32. [PUBMED: 20438718]

Eggermont 2004
Eggermont JJ, Roberts LE. The neuroscience of tinnitus. *Trends in Neurosciences* 2004;**27**(11):676–82. [PUBMED: 15474168]

El-Shunnar 2011
El-Shunnar SK, Hoare DJ, Smith S, Gander PE, Kang S, Fackrell K, et al. Primary care for tinnitus: practice and opinion among GPs in England. *Journal of Evaluation in Clinical Practice* 2011;**17**(4):684–92. [PUBMED: 21707872]

Electronic Medicines Compendium 2015
Electronic Medicines Compendium. Betahistine dihydrochloride 16 mg tablets. https://www.medicines.org.uk/emc/medicine/26617 2015.

Engineer 2011
Engineer ND, Riley JR, Seale JD, Vrana WA, Shetake JA, Sudanagunta SP, et al. Reversing pathological neural activity using targeted plasticity. *Nature* 2011;**470**(7332):101–4. [PUBMED: 21228773]

Fackrell 2017
Fackrell K, Smith H, Colley V, Thacker B, Horobin A, Haider HF, et al. Core Outcome Domains for early phase clinical trials of sound-, psychology-, and pharmacology-based interventions to manage chronic subjective tinnitus in adults: the COMIT'ID study protocol for using a Delphi process and face-to-face meetings to establish consensus. *Trials* 2017;**18**(1):388. [PUBMED: 28835261]

Fowler 1944
Fowler E. Head noises in normal and in disordered ears: significance, measurement, differentiation and treatment. *Archives of Otolaryngology* 1944;**39**(6):498–503.

Fuller 2017
Fuller TE, Haider HF, Kikidis D, Lapira A, Mazurek B, Norena A, et al. Different teams, same conclusions? a systematic review of existing clinical guidelines for the assessment and treatment of tinnitus in adults. *Frontiers in Psychology* 2017;**8**:206. [PUBMED: 28275357]

Furlong 2001
Furlong WJ, Feeny DH, Torrance GW, Barr RD. The Health Utilities Index (HUI) system for assessing health-related quality of life in clinical studies. *Annals of Medicine* 2001;**33**(5):375–84. [PUBMED: 11491197]

Gallus 2015
Gallus S, Lugo A, Garavello W, Bosetti C, Santoro E, Colombo P, et al. Prevalence and determinants of tinnitus in the Italian adult population. *Neuroepidemiology* 2015;**45** (1):12–9. [PUBMED: 26182874]

Guitton 2003
Guitton MJ, Caston J, Ruel J, Johnson RM, Pujol R, Puel JL. Salicylate induces tinnitus through activation of cochlear NMDA receptors. *Journal of Neuroscience* 2003;**23**(9): 3944–52. [PUBMED: 12736364]

Hall 2011
Hall DA, Lainez MJ, Newman CW, Sanchez TG, Egler M, Tennigkeit F, et al. Treatment options for subjective tinnitus: self reports from a sample of general practitioners and ENT physicians within Europe and the USA. *BMC Health Services Research* 2011;**11**:302. [PUBMED: 22053947]

Hall 2018
Hall DA, Fackrell K, Li AB, Thavayogan R, Smith S, Kennedy V, et al. A narrative synthesis of research evidence for tinnitus-related complaints as reported by patients and their significant others. *Health and Quality of Life Outcomes* 2018;**16**(1):61. [PUBMED: 29642913]

Hallam 2009
Hallam RS. *TQ, Manual of the Tinnitus Questionnaire: Revised and Updated*. 2nd Edition. London: Polpresa Press, 2009.

Hamilton 1960
Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* 1960;**23**:56–62. [PUBMED: 14399272]

Han 2009
Han BI, Lee HW, Kim TY, Lim JS, Shin KS. Tinnitus: characteristics, causes, mechanisms, and treatments. *Journal of Clinical Neurology (Seoul, Korea)* 2009;**5**(1):11–9. [PUBMED: 19513328]

Handbook 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hays 1993
Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. *Health Economics* 1993;**2**(3): 217–27. [PUBMED: 8275167]

Henry 2005
Henry JA, Dennis KC, Schechter MA. General review of tinnitus: prevalence, mechanisms, effects, and management. *Journal of Speech, Language, and Hearing Research* 2005;**48** (5):1204–35. [PUBMED: 16411806]

Henry 2008
Henry JA, Zaugg TL, Myers PJ, Schechter MA. The role of audiologic evaluation in progressive audiologic tinnitus management. *Trends in Amplification* 2008;**12**(3):170–87. [PUBMED: 18628281]

Hiller 2006
Hiller W, Goebel G. Factors influencing tinnitus loudness and annoyance. *Archives of Otolaryngology--Head & Neck Surgery* 2006;**132**(12):1323–30. [PUBMED: 17178943]

Hoare 2011
Hoare DJ, Hall DA. Clinical guidelines and practice: a commentary on the complexity of tinnitus management. *Evaluation & the Health Professions* 2011;**34**(4):413–20. [PUBMED: 21177640]

Hoare 2014
Hoare DJ, Edmondson-Jones M, Sereda M, Akeroyd MA, Hall D. Amplification with hearing aids for patients with tinnitus and co-existing hearing loss. *Cochrane Database of Systematic Reviews* 2014, Issue 1. DOI: 10.1002/14651858.CD010151.pub2

James 2001
James AL, Burton MJ. Betahistine for Meniere's disease or syndrome. *Cochrane Database of Systematic Reviews* 2001, Issue 1. DOI: 10.1002/14651858.CD001873

Jastreboff 1988
Jastreboff PJ, Brennan JF, Coleman JK, Sasaki CT. Phantom auditory sensation in rats: an animal model for tinnitus. *Behavioral Neuroscience* 1988;**102**(6):811–22. [PUBMED: 3214530]

Jastreboff 1990
Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neuroscience Research* 1990;**8**(4):221–54. [PUBMED: 2175858]

Jastreboff 2004
Jastreboff PJ, Hazell JWP. *Tinnitus Retraining Therapy*. Cambridge University Press, 2004. DOI: https://doi.org/10.1017/CBO9780511544989

Jeck-Thole 2006
Jeck-Thole S, Wagner W. Betahistine: a retrospective synopsis of safety data. *Drug Safety* 2006;**29**(11):1049–59. [PUBMED: 17061910]

Kluk 2006
Kluk K, Moore BC. Dead regions in the cochlea and enhancement of frequency discrimination: effects of audiogram slope, unilateral versus bilateral loss, and hearing-aid use. *Hearing Research* 2006;**222**(1-2):1–15. [PUBMED: 17071031]

Kuk 1990
Kuk FK, Tyler RS, Russell D, Jordan H. The psychometric properties of a tinnitus handicap questionnaire. *Ear and Hearing* 1990;**11**(6):434–45. [PUBMED: 2073977]

König 2006
König O, Schaette R, Kempter R, Gross M. Course of hearing loss and occurrence of tinnitus. *Hearing Research* 2006;**221**(1-2):59–64. [PUBMED: 16962270]

Lacour 2007
Lacour M, van de Heyning PH, Novotny M, Tighilet B. Betahistine in the treatment of Meniere's disease. *Neuropsychiatric Disease and Treatment* 2007;**3**(4):429–40. [PUBMED: 19300572]

Martines 2010
Martines F, Bentivegna D, Di Piazza F, Martines E, Sciacca V, Martinciglio G. Investigation of tinnitus patients in Italy: clinical and audiological characteristics. *International Journal of Otolaryngology* 2010;**2010**:265861. [PUBMED: 20652075]

Martinez 1972
Martinez DM. The effect of Serc (betahistine hydrochloride) on the circulation of the inner ear in experimental animals. *Acta Oto-laryngologica. Supplementum* 1972;**305**:29–47. [PUBMED: 4353749]

McCormack 2016
McCormack A, Edmondson-Jones M, Somerset S, Hall DA. A systematic review of the reporting of tinnitus prevalence and severity. *Hearing Research* 2016;**337**:70–9. [PUBMED: 27246985]

McDermott 1998
McDermott HJ, Lech M, Kornblum MS, Irvine DR. Loudness perception and frequency discrimination in subjects with steeply sloping hearing loss: possible correlates of neural plasticity. *Journal of the Acoustical Society of America* 1998;**104**(4):2314–25. [PUBMED: 10491696]

McFerran 2018
McFerran D, Hoare DJ, Carr S, Ray J, Stockdale D. Tinnitus services in the United Kingdom: a survey of patient experiences. *BMC Health Services Research* 2018;**18** (1):110. [PUBMED: 29433479]

Meikle 2012
Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, et al. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear and Hearing* 2012;**33**(2):153–76. [PUBMED: 22156949]

Melcher 2013
Melcher JR, Knudson IM, Levine RA. Subcallosal brain structure: correlation with hearing threshold at supra-clinical frequencies (>8 kHz), but not with tinnitus. *Hearing Research* 2013;**295**:79–86. [PUBMED: 22504034]

Middleton 2011
Middleton JW, Kiritani T, Pedersen C, Turner JG, Shepherd GM, Tzounopoulos T. Mice with behavioral evidence of tinnitus exhibit dorsal cochlear nucleus hyperactivity because of decreased GABAergic inhibition. *Proceedings of the National Academy of Sciences of the United States of America* 2011;**108**(18):7601–6. [PUBMED: 21502491]

Moller 2000
Moller AR. Similarities between severe tinnitus and chronic pain. *Journal of the American Academy of Audiology* 2000;**11** (3):115–24. [PUBMED: 10755808]

Moore 2009
Moore BC, Vinay SN. Enhanced discrimination of low-frequency sounds for subjects with high-frequency dead regions. *Brain* 2009;**132**(Pt 2):524–36. [PUBMED: 19036764]

Mulders 2010
Mulders WH, Seluakumaran K, Robertson D. Efferent pathways modulate hyperactivity in inferior colliculus. *Journal of Neuroscience* 2010;**30**(28):9578–87. [PUBMED: 20631186]

Murdin 2016
Murdin L, Hussain K, Schilder AG. Betahistine for symptoms of vertigo. *Cochrane Database of Systematic Reviews* 2016, Issue 6. DOI: 10.1002/14651858.CD010696.pub2

Mühlnickel 1998
Mühlnickel W, Elbert T, Taub E, Flor H. Reorganization of auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences of the United States of America* 1998;**95** (17):10340–3. [PUBMED: 9707649]

Newman 1996
Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. *Archives of Otolaryngology--Head & Neck Surgery* 1996;**122**(2):143–8. [PUBMED: 8630207]

Noreña 2005
Noreña AJ, Eggermont JJ. Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. *Journal of Neuroscience* 2005;**25**(3): 699–705. [PUBMED: 15659607]

Noreña 2011
Noreña AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. *Neuroscience and Biobehavioral Reviews* 2011;**35**(5):1089–109. [PUBMED: 21094182]

Phillips 2008
Phillips JS, Prinsley PR. Prescribing practices for betahistine. *British Journal of Clinical Pharmacology* 2008;**65**(4):470–1. [PUBMED: 18279470]

Pilati 2012
Pilati N, Large C, Forsythe ID, Hamann M. Acoustic over-exposure triggers burst firing in dorsal cochlear nucleus fusiform cells. *Hearing Research* 2012;**283**(1-2):98–106. [PUBMED: 22085487]

Ratnayake 2009
Ratnayake SA, Jayarajan V, Bartlett J. Could an underlying hearing loss be a significant factor in the handicap caused by tinnitus?. *Noise & Health* 2009;**11**(44):156–60. [PUBMED: 19602769]

Rauschecker 1999
Rauschecker JP. Auditory cortical plasticity: a comparison with other sensory systems. *Trends in Nurosciences* 1999;**22** (2):74–80. [PUBMED: 10092047]

Rauschecker 2010
Rauschecker JP, Leaver AM, Muhlau M. Tuning out the noise: limbic-auditory interactions in tinnitus. *Neuron* 2010;**66**(6):819–26. [PUBMED: 20620868]

Reiss 1986
Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour Research and Therapy* 1986;**24**(1): 1–8. [PUBMED: 3947307]

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roberts 2010
Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringing ears: the neuroscience of tinnitus. *Journal of Neuroscience* 2010;**30**(45):14972–9. [PUBMED: 21068300]

Sahley 2001
Sahley TL, Nodar RH. A biochemical model of peripheral tinnitus. *Hearing Research* 2001;**152**(1-2):43–54. [PUBMED: 11223280]

Sanchez 2002
Sanchez TG, Ferrari GMS. The control of tinnitus through hearing aids: suggestions for optimal use. *Pró-Fono Revista de Atualização Científica* 2002;**14**:111–8.

Schaette 2006
Schaette R, Kempter R. Development of tinnitus-related neuronal hyperactivity through homeostatic plasticity after hearing loss: a computational model. *European Journal of Neuroscience* 2006;**23**(11):3124–38. [PUBMED: 16820003]

Schaette 2011
Schaette R, McAlpine D. Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. *Journal of Neuroscience* 2011;**31** (38):13452–7. [PUBMED: 21940438]

Seki 2003
Seki S, Eggermont JJ. Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after

localized tone-induced hearing loss. *Hearing Research* 2003; **180**(1-2):28–38. [PUBMED: 12782350]

Sereda 2011
Sereda M, Hall DA, Bosnyak DJ, Edmondson-Jones M, Roberts LE, Adjamian P, et al. Re-examining the relationship between audiometric profile and tinnitus pitch. *International Journal of Audiology* 2011;**50**(5):303–12. [PUBMED: 21388238]

Sereda 2015
Sereda M, Edmondson-Jones M, Hall DA. Relationship between tinnitus pitch and edge of hearing loss in individuals with a narrow tinnitus bandwidth. *International Journal of Audiology* 2015;**54**(4):249–56. [PUBMED: 25470623]

Skevington 2004
Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Quality of Life Research* 2004;**13**(2):299–310. [PUBMED: 15085902]

Sweetow 1990
Sweetow RW, Levy MC. Tinnitus severity scaling for diagnostic/therapeutic usage. *Hearing Instruments* 1990;**41** (20-1):46.

Tass 2012
Tass PA, Adamchic I, Freund HJ, von Stackelberg T, Hauptmann C. Counteracting tinnitus by acoustic coordinated reset neuromodulation. *Restorative Neurology and Neuroscience* 2012;**30**(2):137–59. [PUBMED: 22414611]

Thai-Van 2002
Thai-Van H, Micheyl C, Norena A, Collet L. Local improvement in auditory frequency discrimination is associated with hearing-loss slope in subjects with cochlear damage. *Brain* 2002;**125**(Pt 3):524–37. [PUBMED: 11872610]

Thai-Van 2003
Thai-Van H, Micheyl C, Moore BC, Collet L. Enhanced frequency discrimination near the hearing loss cut-off: a consequence of central auditory plasticity induced by cochlear damage?. *Brain* 2003;**126**(Pt 10):2235–45. [PUBMED: 12847078]

Timmerman 1994
Timmerman H. Pharmacotherapy of vertigo: any news to be expected?. *Acta Oto-laryngologica. Supplementum* 1994; **513**:28–32. [PUBMED: 7910713]

Tunkel 2014
Tunkel DE, Bauer CA, Sun GH, Rosenfeld RM, Chandrasekhar SS, Cunningham ER Jr, et al. Clinical practice guideline: tinnitus executive summary. *Otolaryngology--Head and Neck Surgery* 2014;**151**(4): 533–41. [PUBMED: 25274374]

van Esch 2018
van Esch B, van der Zaag-Loonen HJ, Bruintjes T, Murdin L, James A, van Benthem PP. Betahistine for Ménière's disease or syndrome. *Cochrane Database of Systematic Reviews* 2018, Issue 1. DOI: 10.1002/14651858.CD012914

Vanneste 2012
Vanneste S, De Ridder D. The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks. *Frontiers in Systems Neuroscience* 2012;**6**:31. [PUBMED: 22586375]

Weisz 2005
Weisz N, Moratti S, Meinzer M, Dohrmann K, Elbert T. Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. *PLoS Medicine* 2005;**2**(6):e153. [PUBMED: 15971936]

Wilson 1991
Wilson PH, Henry J, Bowen M, Haralambous G. Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus. *Journal of Speech and Hearing Research* 1991;**34**(1):197–201. [PUBMED: 2008074]

Zigmond 1983
Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica* 1983;**67**(6): 361–70. [PUBMED: 6880820]

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Examples of questionnaires measuring tinnitus symptom severity

Measurement instrument (author, year)	Number of items and subscales	Internal consistency (Cronbach's alpha for the global score)
Tinnitus Functional Index (Meikle 2012)	25 items, 8 subscales	0.97

Table 1. Examples of questionnaires measuring tinnitus symptom severity (*Continued*)

Tinnitus Handicap Inventory (Newman 1996)	25 items, 3 subscales	0.93
Tinnitus Handicap Questionnaire (Kuk 1990)	27 items, 3 subscales	0.94
Tinnitus Reaction Questionnaire (Wilson 1991)	26 items	0.96
Tinnitus Questionnaire, English version (Hallam 2009)	52 items, 5 subscales	0.94
Tinnitus Questionnaire, German version (Hiller 2006)	52 items, 6 subscales	0.93
Tinnitus Severity Scale (Sweetow 1990)	15 items	Not reported

APPENDICES

Appendix 1. CENTRAL search strategy

1 MESH DESCRIPTOR Tinnitus EXPLODE ALL AND CENTRAL:TARGET
2 (tinnit*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
3 #1 OR #2
4 MESH DESCRIPTOR betahistine EXPLODE ALL AND CENTRAL:TARGET
5 (betahistin* or serc or betaserc):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
6 AEQUAMEN or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL AND CENTRAL:TARGET
7 ((BY next vertin)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
8 (Betavert or vertigon or pt9 or "pt 9"):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
9 #4 OR #5 OR #6 OR #7 OR #8
10 #3 AND #9

CONTRIBUTIONS OF AUTHORS

DAH conceived the study and drafted the protocol. All authors contributed to the design and critically revised the protocol for important intellectual content.

Planned author contributions to the full review:

The Cochrane ENT Information Specialist will develop and run the search strategy.

DAH will obtain copies of studies with assistance from the NIHR Nottingham Biomedical Research Centre.

DAH, DM and IS will be responsible for selection of studies.

DAH, IW and DS will be responsible for data extraction.

IW and IS will be responsible for assessing risk of bias.

IW will enter data into RevMan.

IW, DS and IS will conduct and interpret the analysis.

IW, IS and DAH will draft the final review.

DAH, DS and IS will be responsible for updating the review.

DECLARATIONS OF INTEREST

Deborah A Hall: DAH is an NIHR Senior Investigator and Section Editor for the journal *Hearing Research*, Elsevier. She leads the Core Outcome Measures in Tinnitus (COMiT) initiative whose work is currently supported by the European Union's Horizon 2020

research and innovation programme under the Marie Skł odowska-Curie grant agreement No 764604 and the NIHR Nottingham Biomedical Research Centre.

Inge Wegner: none known.

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Don McFerran: receives royalties for writing books on tinnitus has received consultancy honoraria from GlaxoSmithKline, Autifony and Otonomy.

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