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Sound therapy (using amplification devices and/or sound generators) for tinnitus in adults (Protocol)

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[Intervention Protocol]

Sound therapy (using amplification devices and/or sound generators) for tinnitus in adults

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ABSTRACT

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

To assess the effects of sound therapy (using amplification devices and/or sound generators) for tinnitus in adults.

BACKGROUND

This is a new protocol for an update of two Cochrane Reviews on sound therapy (masking) and on amplification with hearing aids for tinnitus that were first published in the *Cochrane Library* in Issue 12, 2010 and updated in 2012 (Hobson 2012) and in Issue 1, 2014 (Hoare 2014), respectively. The following paragraphs and Description of the condition are based on the latter Cochrane Review 'Amplification with hearing aids for patients with tinnitus and co-existing hearing loss' and are reproduced with permission (Hoare 2014).

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 be also 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 tinnitus is co-morbid with some degree of measurable 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).

An important implication in clinical research is that outcome measures need to distinguish benefits specific to improved hearing from those specific to improvement in the psychological aspects of tinnitus.

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 specialisms of the authors or differences in the clinical specialisms 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 2010; Cima 2012; Department of Health 2009; Hall 2011; Henry 2008; Hoare 2011). Common across all these documents, however, is the use or recommendation of written questionnaires to assess tinnitus and its impact on patients and their families 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 (depression or anxiety). Assessment of the perceptual characteristics of tinnitus (pitch, loudness, minimum masking level) and residual inhibition are also recommended (Cima 2018). Although these measures do not correlate well with tinnitus symptom severity (Hiller 2006), they can prove useful in patient counselling (Henry 2004), as a baseline before start of treatment (El Refaie 2004), or by demonstrating stability of the tinnitus percept over time (Department of Health 2009).

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 insomnia, 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

Most 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; Muhlnickel 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; Norena 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 Norena 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 (Norena 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, Konig 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 2015a).

Description of the intervention

Amplification devices (hearing aids)

The following description of hearing aids is taken from the Cochrane Review 'Amplification with hearing aids for patients with tinnitus and co-existing hearing loss' and reproduced with permission Hoare 2014.
The standard function of a hearing aid is to amplify and modulate sound, primarily for the purpose of making sound more accessible and aiding communication. Using hearing aids in tinnitus management has been proposed as a useful strategy since the 1940s (Saltzman 1947), although benefit reportedly varies and there is no clear consensus on when a person would or would not benefit from amplification (Henry 2005; Hoare 2012). Beck 2011 proposes that hearing aid fittings for people with very mild up to moderate sensorineural hearing loss (who might not ordinarily look for or be prescribed a hearing aid) can lead to significant improvements in tinnitus. Currently, hearing aids, supplemented with education and advice, form a common intervention for someone who has tinnitus and an aidable hearing loss (Hoare 2012; Sereda 2015). This combination of hearing aid provision with education and advice might be considered a complex intervention with interdependent components (Shepperd 2009).
There are many options for hearing aid fitting that complicate their use in tinnitus. For example, Del Bo 2007 suggests that the best clinical result for someone with tinnitus requires binaural amplification. Trotter 2008, however, in describing a 25-year experience of hearing aids in tinnitus therapy found no difference in tinnitus improvement between unilaterally and bilaterally aided patients.
For other aspects of hearing aid fitting there appears greater consensus, such as the value of using open-fitting aids (if acoustically suitable), which allow natural environmental sound to enter the ear, as well as amplifying those sounds, thus improving perceived sound quality (Del Bo 2007; Forti 2010).
The bandwidth amplified by the hearing aid may also be important to its effect on tinnitus. In a study by Moffat 2009 the tinnitus percept was not at all affected in a group receiving high-bandwidth amplification, which had less gain at frequencies below 1 kHz and more gain at frequencies above 1 kHz than conventional amplification. In a group receiving conventional amplification, however, there was a significant reduction of the contribution of all low-frequency components of the measured tinnitus spectrum to matched tinnitus. This suggests an interaction between the perceptual characteristics of tinnitus and the pattern of sensory inputs in this group.
Finally, hearing aid prescription might also be combined with other forms of therapy such as formal counselling, albeit with mixed evidence for the efficacy of such combinations of therapies (Hiller 2005; Searchfield 2010).

Sound generator devices

Sound generators are ear-level devices that produce sounds for therapeutic use.
Sound generator devices were introduced in 1976, on the principle of distraction, turning complete masking of tinnitus with white noise into a clinical management technique (Vernon 1976). The purpose of the 'masking' method was described by Vernon as making the tinnitus inaudible with a more acceptable sound (Vernon 1976; Vernon 1977). With the introduction of combination hearing aids partial masking became an acceptable outcome of the sound therapy. Partial masking provided only partial reduction in tinnitus, meaning that the tinnitus could still be heard but in a suppressed form (Vernon 1988).
Current views on sound generators acknowledge that masking is only one of the goals of sound therapy, alongside achieving tinnitus relief (i.e. reduction in tinnitus annoyance) regardless of the mechanism by which it is achieved (complete masking, partial masking or not masking the tinnitus; Henry 2008a). Other philosophies include the use of noise as a form of sound enrichment, counteracting the effects of sensory deprivation (Jastreboff 1993).
Recommendations regarding choice of sounds or level of sound that should be used vary across the literature and often strongly depend on the management programme followed. For example, tinnitus masking (TM) permits the use of any sound that provides maximum masking benefit (Henry 2002). The choice of sound,

therefore, is based on a combination of effectiveness and acceptability for the patient. On the other hand, tinnitus retraining therapy (TRT) recommends the use of broadband noise to be adjusted to a 'mixing' or 'blending' point (Jastreboff 2007; Korres 2010; McFerran 2009), or below that level (Jastreboff 2006), to allow for habituation.

Many studies describe sound therapy in the context of a larger management programme, combining multiple approaches to manage tinnitus, where the counselling component plays a major role (e.g. Progressive Tinnitus Management, TRT, Neuromonics). It is therefore often difficult or even impossible to draw conclusions specific to the sound therapy component of the programme. It is possible that other components, rather than the devices, might have played a role in the observed improvements in tinnitus distress or handicap.

Combination hearing aids

Combination hearing aids combine amplification and sound generation options within one device, and new generations of such devices offer the same quality of amplification as 'standard' hearing aids (Henry 2004a; Sereda 2017; Tutaj 2018).

How the intervention might work

Hearing aids may be beneficial for people with tinnitus in a number of ways. The amplification of external sounds may reverse or reduce the drive responsible for 'pathological' changes in the central auditory system associated with hearing loss, such as increased gain or auditory cortex reorganisation, possibly by strengthening lateral inhibitory connections. Increased neuronal activity that results from amplified sounds may reduce the contrast between tinnitus activity and background activity thus reducing the audibility and awareness of tinnitus. Alternatively, amplification may simply refocus attention on alternative auditory stimuli that are incompatible and unrelated to the tinnitus sound. As the main function of hearing aids is to improve communication, for many people this inherently reduces stress and anxiety (Carmen 2002; Surr 1985), and so may indirectly affect improvements in tinnitus report. Finally, it is unquestioned that there is the potential for a large placebo effect in any study of tinnitus (Dobie 1999), and so it is essential that any investigation of hearing aids for tinnitus considers the potential impact of this effect.

Postulated mechanisms through which sound generators may be beneficial for tinnitus include tinnitus masking by reducing audibility (Vernon 1977) or by inducing a sense of relief (Vernon 2000), through habituation (Jastreboff 1993), by reversing abnormal cortical reorganisation or activity thought to contribute to tinnitus (Norena 2005; Tass 2012), or through the promotion of relaxation (Sweetow 2010).

Combination hearing aids combine the above approaches within one device (Tutaj 2018).

Potential modifiers of treatment outcome include the presence of hearing loss, clinically significant anxiety or depression, or high levels of tinnitus distress (which may be intractable to sound therapy alone) (Hoare 2012; Hoare 2014a; Jastreboff 2004; Searchfield 2010; Searchfield 2017).

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. Hearing aids, sound generators and combination devices (amplification aid sound generation within one device) are a component of many tinnitus management programmes and together with information and advice are a first line of management in UK audiology departments for someone who has tinnitus (Hoare 2014; Hobson 2012; Sereda 2015; Tutaj 2018). These options are also subject to ongoing research and development, for example to examine the effectiveness of new technologies such as mobile applications, wireless streaming and alternative sound options such as 3D sounds (Tutaj 2018).

Two previous Cochrane Reviews concluded that there was a lack of evidence for the effectiveness of these management options (Hobson 2012; Hoare 2014). The first review looked at sound therapy (masking) in the management of tinnitus in adults (Hobson 2012). The methods and searches in that review are now outdated, as is the use of term 'masking' as the only suggested mechanism of action for sound therapy. The second review looked at amplification with hearing aids for patients with tinnitus and co-existing hearing loss and an update of that review is now due (Hoare 2014). The current review will provide an update to both of these Cochrane Reviews and extend them to separately consider the specific effects and safety of the three different sound therapy options.

OBJECTIVES

To assess the effects of sound therapy (using amplification devices and/or sound generators) for tinnitus in adults.

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

Adults (≥ 18 years) with acute or chronic subjective idiopathic tinnitus.

Types of interventions

Amplification-only devices, sound generators and combination devices (combined amplification and sound generation).
The comparators are amplification only, sound generator only and combination device.
The main comparison pair(s) will be:

- amplification only *versus* waiting list control *or* placebo *or* education/information only with no device;
- sound generator only *versus* waiting list control *or* placebo *or* education/information only with no device;
- combination device *versus* waiting list control *or* placebo *or* education/information only with no device.

Other possible comparison pairs include:

- amplification only *versus* sound generator only;
- combination device *versus* amplification only;
- combination device *versus* sound generator only.

We will exclude studies that have complex interventions, which explicitly include a sound therapy and other non-sound components (e.g. psychotherapy) as a part of a programme (e.g. Neuromonics). We will also exclude studies of neuromodulation (desynchronisation) devices (reviewed in Hoare 2015).

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 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 Questionnaire (Hallam 1996; Hiller 1992);
    - Tinnitus Functional Index (Meikle 2012);
    - Tinnitus Handicap Inventory (Newman 1996);
    - Tinnitus Handicap Questionnaire (Kuk 1990);
    - Tinnitus Reaction Questionnaire (Wilson 1991);
    - Tinnitus Severity Scale (Sweetow 1990).

We will update this list on an ongoing basis whenever other questionnaires are introduced.

- Significant adverse effect: increase in self-reported tinnitus loudness.

Secondary outcomes

- Depressive symptoms or depression as measured by a validated instrument, such as the Beck Depression Inventory (Beck 1988; Beck 1996), the depression scale of the Hospital Anxiety and Depression Scale (HADS; Zigmond 1983), and the Hamilton Rating Scale for Depression (Hamilton 1960).
- Anxiety symptoms or generalised anxiety as measured by a validated instrument, such as the anxiety scale of the Beck Anxiety Inventory (Beck 1988), the anxiety scale of the HADS (Zigmond 1983), or the Anxiety Sensitivity Index (Reiss 1986).
- Health-related quality of life as measured by a validated instrument, such as the Short-Form 36 (Hays 1993), WHOQOLBREF (Skevington 2004), other WHOQOL versions or Health Utilities Index (Furlong 2001).
- Adverse effects associated with wearing the device such as pain, discomfort, tenderness or skin irritation, or ear infections.

In addition, where possible we will report the newly developed core outcomes for trials of sound therapy for tinnitus, these being **tinnitus intrusiveness**, **ability to ignore**, **concentration**, **quality of sleep** and **sense of control** (Fackrell 2017).
We will aim to measure long-term effects at three to 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);
- Ovid PsycINFO (1806 to date);
- EBSCO CINAHL (1982 to date);
- Web of Knowledge, Web of Science (1945 to date);
- LILACS (Latin American and Caribbean Health Science Information database; 1982 to date);

- ClinicalTrials.gov (search via the Cochrane Register of Studies and www.clinicaltrials.gov 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 strategies detailed in 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 sound therapy (using amplification devices and/or sound generators) for tinnitus. We will consider adverse effects described in the included studies only.

Data collection and analysis

Selection of studies

Three authors (MS, AER and DAH) will independently review all studies retrieved to determine their eligibility for inclusion in the review. The authors will then review the full-text articles of the retrieved studies and apply the inclusion criteria independently. Any disagreements will be discussed between all three authors until a consensus is reached.

Data extraction and management

MS, DJH, AER and JX will independently extract data using a purposefully designed data extraction form. 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 study authors for further information.
Information to be extracted will include: study design, setting, methods or randomisation and blinding, power, inclusion and exclusion criteria, type of intervention and control, treatment duration, treatment fidelity, type and duration of follow-up, and outcome measures and statistical tests.
Data to be extracted will include: baseline characteristics of participants (age, sex, duration of tinnitus, tinnitus symptom severity, tinnitus loudness and pitch 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.
We will also contact authors where further information is required that is not contained within the study 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, the authors will make and agree numeric estimates.
After independent data extraction by MS, DJH, AER and JX, 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

MS, DJH, AER and JX 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.

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

We will analyse dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs). We will summarise continuous outcomes as mean difference (MD) with 95% CI. We will use standardised mean difference (SMD) (Cohen's d effect size (ES)) when different scales of measurement have been used to measure the same outcome. A positive effect size indicates that the treatment group achieved better outcomes than the control group.

Unit of analysis issues

For parallel-group RCTs the unit of analysis will be the group mean. However, some studies included in the review may involve clustering (for example, a group counselling intervention) or compare more than two intervention groups. To avoid unit of analysis errors we will consider alternative analyses for cluster-randomised trials and for studies with more than two intervention groups. For cluster-randomised trials we will adopt approximate analyses - effective sample sizes (Donner 2002). For studies with more than two intervention groups, we will either combine groups to create a single pair-wise comparison or, if this is not appropriate, select the most relevant pair of interventions for comparison.

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 assess studies for clinical, statistical and methodological heterogeneity. We will quantify statistical heterogeneity using the I^2 statistic and the Chi^2 test. An approximate guide to interpretation of the I^2 statistic is provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). An I^2 value of 50% or higher may represent substantial or considerable heterogeneity. Where Chi^2 is greater than the degrees of freedom (K-1 degrees of freedom, where K is the number of studies), then heterogeneity is likely to be present. We will consider heterogeneity to be statistically significant if the P value is less than 0.10. 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

For each sound therapy intervention, we will investigate potential publication bias and the influence of individual studies on the overall outcome identified in this review. 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

We will analyse separately the different sound therapy options (amplification only, sound generation only, combined amplification and sound generation) and different durations of tinnitus (acute and chronic). 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 randomised controlled trials using a fixed-effect model, except when heterogeneity is found. We will pool dichotomous data using the RR measure. 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 outcome instruments with regard to their suitability for pooling. For meta-analyses on the primary outcome (tinnitus symptom severity), 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 symptom severity (high convergent validity) and show a similar direction of treatment-related effect. We will take the same approach for secondary outcomes.

Network meta-analysis

Firstly, when studies are homogenous we will perform a head to head pair-wise meta-analysis using a random-effects model using STATA version 13 to estimate the absolute or relative measures depending upon the outcome measure. For continuous data we will use the SMD or Cohen's d due to the various tools used for measuring the same outcomes. For dichotomous outcomes we will use risk ratios and 95% CI. We will perform network meta-analysis within a frequentist framework using the mvmeta command in STATA version 13 (Chaimani 2013). We will assume a common heterogeneity variance across the different interventions. We will

also evaluate the assumption of transitivity by looking at the distribution of the possible effect modifier and the baseline variables of included studies in each network (Salanti 2009).

We will conduct a network plot to access the connection between the interventions for each outcome. NMA combines direct and indirect evidence for all relative treatment effects and can therefore provide estimates with maximum power and increased precision (Salanti 2008). In NMA we assume any participants in the included studies will have an equally likely chance to be randomised to any of the treatment options. When studies follow the transitivity assumption, we will conduct a multivariate random effect NMA for each outcome. We will present the result of all comparisons in a league table. To obtain the ranking probabilities of each treatment we will use the surface under the cumulative ranking (SUCRA) and the rankongram (Salanti 2011).

We will assess the agreement between direct and indirect evidence measured as inconsistency employing the local and global method. We will use the loop-specific approach method to evaluate the consistency assumption in each closed loop to calculate the inconsistency factor. Then, we will use the magnitude of the inconsistency factors and their 95% CIs to infer the presence of inconsistency in each loop (Salanti 2009). We will use the 'design-by-treatment' model approach (Handbook 2011; Higgins 2012) to measure the different sources of inconsistency in the entire network based on the Chi^2 test (Veroniki 2013).

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will carry out subgroup analyses to explore potential effect modifiers. This will be restricted to a very small number of subgroups. The planned subgroups are defined by:

- presence or absence of hearing loss (cut-off defined according to pure tone average of 20 dB at 0.5, 1, 2 and 4 kHz);
- baseline tinnitus symptom severity (where the questionnaire has a validated grading system to differentiate mild/moderate and severe tinnitus);
- baseline anxiety or depression (presence or absence as defined by the cut-off score on a validated questionnaire measure).

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

Three independent authors (MS, DJH and JX) 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;
- publication bias.

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

- Amplification only *versus* waiting list control, placebo, education/information only with no device.
- Sound generator only *versus* waiting list control, placebo, education/information only with no device.
- Combination devices *versus* waiting list control, placebo, education/information only with no device, amplification only, sound generator only.

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

- tinnitus symptom severity;
- significant adverse effect (increase in self-reported tinnitus loudness);
- depression;
- anxiety;
- health-related quality of life;
- adverse effects associated with wearing the device.

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* *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 global score)
Tinnitus Functional Index (Meikle 2012)	25 items, 8 subscales	a = 0.97
Tinnitus Handicap Inventory (Newman 1996)	25 items, 3 subscales	a = 0.93
Tinnitus Handicap Questionnaire (Kuk 1990)	27 items, 3 subscales	a = 0.94
Tinnitus Questionnaire (Hallam 1996)	52 items, 5 subscales	a = 0.94
Tinnitus Reaction Questionnaire (Wilson 1991)	26 items, 4 subscales	a = 0.96
Tinnitus Severity Scale (Sweetow 1990)	15 items	Not reported

APPENDICES

Appendix 1. Search strategies

CENTRAL (CRS)	MEDLINE (Ovid)	Embase (Ovid)
1 MESH DESCRIPTOR Tinnitus EXPLODE ALL AND CENTRAL:TARGET 2 (tinnit*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 1 3 #1 OR #2 AND CENTRAL:TARGET 4 MESH DESCRIPTOR Hearing Aids EXPLODE ALL AND CENTRAL:TARGET 5 MESH DESCRIPTOR Perceptual Masking EXPLODE ALL AND CENTRAL:TARGET 6 MESH DESCRIPTOR Acoustic Stimulation EXPLODE ALL AND CENTRAL:TARGET 7 MESH DESCRIPTOR Combined	1. exp Tinnitus/ 2. tinnit*.ab,ti. 3. 1 or 2 4. exp Hearing Aids/ 5. exp Perceptual Masking/ 6. exp Acoustic Stimulation/ 7. Combined Modality Therapy/ 8. exp Music Therapy/ 9. SOUND/th, tu [Therapy, Therapeutic Use] 10. (((hearing or tinnitus) adj3 aid?) or earmold? or (ear adj3 mold?)).ab,ti 11. (mask* or amplification).ab,ti. 12. ("therapeutic sound?" or "therapeutic noise?" or "white noise?" or "tinnitus in-	1. exp tinnitus/ 2. tinnit*.ab,ti. 3. 1 or 2 4. exp hearing aid/ 5. exp auditory stimulation/ 6. exp music therapy/ 7. exp auditory masking/ 8. (((hearing or tinnitus) adj3 aid?) or earmold? or (ear adj3 mold?)).ab,ti 9. (mask* or amplification).ab,ti. 10. ("therapeutic sound?" or "therapeutic noise?" or "white noise?" or "tinnitus instrument?" or "combination instrument?" or "combination device?" or "static noise?" or "tinnitus device?" or "relief product?" or

(*Continued*)

Modality Therapy AND CENTRAL:TARGET
8 MESH DESCRIPTOR Music Therapy EXPLODE ALL AND CENTRAL:TARGET
9 MESH DESCRIPTOR Sound WITH QUALIFIER TU,TH AND CENTRAL:TARGET
10 (((hearing or tinnitus) NEAR (aid or aids)) or earmold* or (ear NEAR mold*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 657
11 (mask* or amplification):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
12 ("therapeutic sound*" or "therapeutic noise*" or "white noise*" or "tinnitus instrument*" or "combination instrument*" or "combination device*" or "static noise*" or "tinnitus device*" or "relief product*" or "puretone device*" or "puretone tinnitus" or "tinnitus system*"):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
13 (tinnitech* OR starkey* OR ultraquiet* or LTWN or MML or TCI or TRD or hisonic* or oticon or phonak or ReSound or widex or siemens or audeo or alta or zen or danalogic or audimed or ipod):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
14 ((auditory or audio or acoustic or noise* or sound* or music or audio) NEAR (stimulat* or generator? or device? or frequency or stimulus)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
15 ((noise* or sound* or music) near (therap* or training or treatment? or frequency or intervention?)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
16 (tinnitus near pitch* near match*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET
17 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 AND CENTRAL:TARGET
18 #17 AND #3 AND CENTRAL:TARGET

strument?" or "combination instrument?" or "combination device?" or "static noise?" or "tinnitus device?" or "relief product?" or "puretone device?" or "puretone tinnitus" or "tinnitus system?").ab,ti
13. (tinnitech* or starkey* or ultraquiet* or LTWN or MML or TCI or TRD or hisonic* or oticon or phonak or ReSound or widex or siemens or audeo or alta or zen or danalogic or audimed or ipod).ab,ti
14. ((auditory or audio or acoustic or noise? or sound? or music or audio) adj3 (stimulat* or generator? or device? or frequency or stimulus)).ab,ti
15. ((noise? or sound? or music) adj3 (therap*or training or treatment? or frequency or intervention?)).ab,ti
16 (tinnitus adj3 pitch* adj3 match*).ab,ti.
17. or/4-16
18. 3 and 17
19. randomized controlled trial.pt.
20. controlled clinical trial.pt.
21. randomized.ab.
22. placebo.ab.
23. drug therapy.fs.
24. randomly.ab.
25. trial.ab.
26. groups.ab.
27. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
28. exp animals/ not humans.sh.
29. 27 not 28
30. 18 and 98 491

"puretone device?" or "puretone tinnitus" or "tinnitus system?").ab,ti
11. (tinnitech* or starkey* or ultraquiet* or LTWN or MML or TCI or TRD or hisonic* or oticon or phonak or ReSound or widex or siemens or audeo or alta or zen or danalogic or audimed or ipod).ab,ti
12. ((auditory or audio or acoustic or noise? or sound? or music or audio) adj3 (stimulat* or generator? or device? or frequency or stimulus)).ab,ti
13. ((noise? or sound? or music) adj3 (therap*or training or treatment? or frequency or intervention?)).ab,ti
14. (tinnitus adj3 pitch* adj3 match*).ab,ti.
15. or/4-14
16. 3 and 15
17. (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw
18. (control* adj group*).tw.
19. (trial* and (control* or comparative)).tw.
20. ((blind* or mask*) and (single or double or triple or treble)).tw
21. (treatment adj arm*).tw.
22. (control* adj group*).tw.
23. (phase adj (III or three)).tw.
24. (versus or vs).tw.
25. rct.tw.
26. crossover procedure/
27. double blind procedure/
28. single blind procedure/
29. randomization/
30. placebo/
31. exp clinical trial/
32. parallel design/
33. Latin square design/
34. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/
36. exp human/
37. 35 not 36
38. 34 not 37
39. 16 and 38 512

(*Continued*)

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CONTRIBUTIONS OF AUTHORS

MS and DJH conceived and all authors contributed to the design of the study. MS drafted the protocol. JX drafted the network meta-analysis section. All authors 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.

MS will obtain copies of studies with the assistance of the University of Nottingham library.

MS, AER and DAH will be responsible for selection of studies.

MS, DJH, AER and JX will be responsible for data extraction.

MS, DJH, AER and JX will be responsible for assessing risk of bias.

MS will enter data into RevMan.

MS, JX and a statistician will conduct the analysis.

MS, DJH and JX will interpret the analysis.

MS, DJH and JX will draft the final review.

MS and DJH will be responsible for updating the review.

DECLARATIONS OF INTEREST

Magdalena Sereda: MS is funded through the British Tinnitus Association Senior Research Fellow/Head of Research Fellowship. MS is Chief Investigator on NIHR Research for Patient Benefit grant 'Feasibility of conducting a multi-centre RCT to assess effectiveness and cost-effectiveness of digital hearing aids in patients with tinnitus and hearing loss'. MS is a member of the Steering Committee for British Society of Audiology Tinnitus and Hyperacusis Special Interest Group and leading on the development of the BSA recommended procedure for candidacy and fitting of combination hearing aids. MS is a Principal Investigator on the British Society of Audiology Applied Research Grant supporting the development of the recommended procedure.

Jun Xia: none known.

Amr El Refaie: none known.

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.

Derek J Hoare: DJH is Associate Editor for the *International Journal of Audiology* and *BMC Health Services Research*, and Chair of the British Society of Audiology tinnitus and hyperacusis special interest group. He is funded by the NIHR and research lead for tinnitus and hyperacusis at the NIHR Nottingham Biomedical Research Centre. He has received tinnitus research funding from the British Society of Audiology, the British Tinnitus Association and the NIHR.

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