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A process for prioritising systematic reviews in tinnitus

Technical report

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ABSTRACT

Objective: To develop an innovative prioritisation process to identify topics for new or updated systematic reviews of tinnitus research.

Design: A two stage prioritisation process was devised. Firstly, a scoping review assessed the amount of randomised-controlled-trial-level evidence available. This enabled development of selection criteria for future reviews, aided the design of template protocol, and suggested the scale of work that would be required to conduct these reviews. Secondly, using the pre-defined primary and secondary criteria, interventions were prioritised for systematic review.

Study sample: Searches identified 1080 records. After removal of duplicates and out of scope works, 437 records remained for full data charting.

Results: The process was tested, using subjective tinnitus as the clinical condition and using Cochrane as the systematic review platform. The criteria produced by this process identified three high priority reviews: 1) Sound therapy using amplification devices and/or sound generators; 2) Betahistine, and 3) Cognitive Behaviour Therapy. Further secondary priorities were: 4) Gingko biloba, 5) Anxiolytics, 6) Hypnotics, 7) Antiepileptics, and 8) Neuromodulation.

Conclusions: A process was developed which successfully identified priority areas for Cochrane systematic reviews of interventions for subjective tinnitus. This technique could easily be transferred to other conditions and other types of systematic reviews.

Keywords: Cochrane, systematic review, priority, management, treatment, tinnitus

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INTRODUCTION

Systematic reviews and meta-analyses represent the highest level of evidence for the effectiveness of clinical interventions and hold a critical place in informing health policy and evidence-based practice (Greenwell et al.2016; Morata et al., 2017). One of the foremost organisations producing systematic reviews is Cochrane, which is a UK based charity (not-for-profit organisation) that supervises a global independent network of healthcare practitioners, researchers, patient advocates and others. It represents more than 11,000 members and over 68,000 supporters from over 130 countries (https://www.cochrane.org/about-us). Cochrane authors conduct systematic reviews of health-care interventions and diagnostic tests which are published as Cochrane Reviews in the Cochrane Library. Previously, Cochrane authors self-selected topics for their reviews and submitted proposals to Cochrane for approval. This process has been updated and now, Cochrane groups are encouraged to work strategically to respond to the needs of funders and key stakeholders to produce reviews on topics of the highest priority to users. One approach to prioritising these reviews is to conduct a scoping exercise (https://ent.cochrane.org/our-evidence/prioritisation/scoping-projects). Cochrane Ear, Nose, & Throat Disorders (Cochrane ENT) group this has developed suites of reviews with an "optimal, shared protocol with a well-designed and consistent set of outcome measures" (Cochrane ENT Group, 2019).

In this report we describe a comprehensive exercise used to prioritise systematic reviews of interventions for tinnitus conducted for the Cochrane ENT group.

Subjective tinnitus is described as the perception of sound in the absence of an external sound source (Jastreboff and Hazell, 2004). It is a symptom experienced by 10-30% of the adult population (McCormack et al., 2016). About 20% of people with tinnitus experience it as

bothersome (McCormack et al., 2016). Problems associated with tinnitus include sleep disturbances, hearing difficulties, difficulties with concentration, social isolation, anxiety, depression, and emotional difficulties such as irritation or stress (Davis and El Refaie, 2000). It is estimated that the prevalence of tinnitus in those adults seeking medical help for hearing problems is as high as 85% (Axelsson and Ringdahl, 1989; Davis and El Refaie, 2000; Meikle and Taylor-Walsh, 1984).

Tinnitus represents a major financial burden to the healthcare system. For example, in England there are approximately 0.75 million primary care consultations each year where the primary complaint is tinnitus (El-Shunnar et al., 2011) and the average cost to the National Health System of tinnitus treatment per year is estimated to be GB£750M. The estimated annual societal costs of tinnitus in the UK is GB£2.7 billion (Stockdale et al., 2017).

There is currently no gold standard treatment for tinnitus, rather, various management strategies are used or have been trialled. Those include education and information, sound-based interventions, psychology-based interventions, self-help interventions, relaxation therapy, pharmacology-based interventions, manual physical therapy, magnetic stimulation, electrical stimulation, complementary and alternative therapies, and combination of two or more approaches (complex interventions). Guidelines for the management of tinnitus have been developed in the USA and Europe (Cima et al., 2019; Fuller et al., 2017a). In the UK, there are commissioning guidelines for tinnitus services for adults (Department of Health, 2009), and clinical practice guidance for the assessment and management of tinnitus in children (British Society of Audiology, 2015) A Clinical Knowledge Summary has been produced by the National Institute for Health and Care Excellence (NICE) and two national guidelines are in development: the first by NICE; the second by the British Society of Audiology (BSA). NICE has published the scope of the guidelines that are in development (https://www.nice.org.uk/guidance/gid-ng10077/documents/final-scope) outlining which

factors will and will not be considered by the guidelines. Effective guidelines can only be developed if there is strong evidence-based information available. If such high-level evidence is not available, recommendations arising from the guidelines are weak and clinically ineffective. These are just some of the drivers for prioritising new and updating existing Cochrane systematic reviews of interventions for tinnitus.

METHODS

The prioritisation process was conducted in two stages. First, a scoping review was conducted to estimate the volume of randomised controlled trial (RCT) level evidence available, to facilitate prioritisation, to aid in the design of a template protocol, and to estimate the work involved in conducting a suite of priority reviews. Secondly, interventions were prioritised for review according to a set of pre-defined criteria.

Scoping review

We followed the methodological framework of Arksey and O'Malley (2005). This consisted of: (1) identifying potentially relevant records; (2) selecting relevant records; (3) extracting data items; and (4) collating, summarising, and reporting the results. The PRISMA-ScR checklist (Tricco et al., 2018) guided reporting of the methods and results of the scoping review.

Search strategy

In July 2017 we conducted a search of the Cochrane ENT Trials Register (via the Cochrane Register of studies) for RCTs. There were no language, publication year, or publication status restrictions. The search was run in the Cochrane ENT Register

(https://ent.cochrane.org/resources/searching-studies/cochrane-ent-trials-register) using the following strategy:

1 MESH DESCRIPTOR Tinnitus EXPLODE ALL AND INREGISTER

2 tinnit* AND INREGISTER

3 #1 OR #2 AND INREGISTER,

where MESH DESCRIPTOR – Medical Subject Headings: The National Library of Medicine controlled vocabulary thesaurus, INREGISTER – in the Cochrane ENT register, EXPLODE ALL – search for selected subject heading (Tinnitus) and all of the subject headings in its family.

The Cochrane ENT Register is populated using the methods described on the Cochrane ENT website (https://ent.cochrane.org/resources/searching-studies/cochrane-ent-trials-register).

We also searched the Cochrane database of Systematic Reviews for all published reviews and protocols for Cochrane reviews with 'tinnitus' in the title.

Selection of studies

Three authors (MS, DJH, DAH) independently screened all abstracts to determine eligibility for inclusion in the scoping review. Records were carried forward for full screening if at least one of the authors selected it. We considered multiple articles reporting the same trial together as a single record. Disagreements were discussed between authors until a consensus was reached. Records were considered for inclusion according to PICOS (Methley et al., 2014), as follows:

***P**opulation:* Children and/or adults with subjective tinnitus

***I**ntervention:* All interventions for subjective tinnitus

***C**omparator:* No intervention (e.g. waiting list), different intervention, placebo

Outcome: Did not form an inclusion criterion

Study design: Randomised controlled trials only.

Data extraction

Data were extracted using a bespoke template form designed by the authors (MS and DJH), piloted on a subset of records, and revised before formal data extraction was undertaken. PICOS data were extracted (population, intervention, comparator, outcomes, and outcome measures used, and study design). Two authors independently extracted the data.

For each intervention, we recorded whether there were existing RCTs, the number of RCTs, and whether those RCTs were included or not in existing Cochrane reviews. In scoping the literature, drug trials were catalogued (by DMcF) according to the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical (ATC) Classification System (https://www.whocc.no/atc_ddd_index/).

Methodological assessment of published Cochrane reviews

A list of published Cochrane systematic reviews and published Cochrane protocols was populated. When judging whether an existing Cochrane systematic review required updating or replacing, we considered the date of the most recent literature search of the review, and whether ongoing studies were identified in those reviews. Both of these factors were used to consider whether there was new research that may alter the estimates of effect, the quality of the overall evidence, or the conclusions drawn in the published review. Other methodological aspects of the systematic reviews were assessed including (1) whether a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram was included; (2) whether the latest risk of bias tool was used; (3) whether a 'Summary of Findings (SoF)' table was included; (4) whether the 'Grading of Recommendations, Assessment,

Development and Evaluation' (GRADE; https://gradepro.org/) tool was used (Schünemann et al., 2013); (5) whether the assessed outcomes included measures of benefits and harms of the intervention; and (6) whether the review included all of the methods sections currently recommended by Cochrane (Higgins and Green, 2011).

Prioritisation process

Authors of this scoping review were experts in tinnitus (clinical researchers, a psychologist, ENT surgeon, and an audiologist) or experts in Cochrane systematic review methodology. All authors took part in agreeing the criteria that were used to prioritise reviews. Firstly a list of criteria was populated including criteria formulated according to the remit from National Institute for Health Research (NIHR) with additional criteria proposed by individual authors. Secondly authors ranked these criteria in order of importance. Based on the ranking, four primary and four secondary criteria were formulated.

Primary criteria were whether:

1. the intervention was available for tinnitus management within the National Health Service (NHS) When considering drug treatments for tinnitus, this included drugs that were used on-licence such as betahistine for Ménière's disease-associated tinnitus. It also included drugs used that have been recorded as being used off-licence as a primary tinnitus treatment (Langguth et al., 2009; Hall et al., 2011; McFerran et al., 2018). It did not include drugs used primarily for treating comorbid conditions.
2. the intervention was included in the NICE document, *Guidelines scope. Tinnitus: assessment and management.* (https://www.nice.org.uk/guidance/gid-ng10077/documents/final-scope). This document outlined the proposed contents of the forthcoming NICE Guideline.

3. there was 'no recommendation' or disagreement in recommendations for an intervention within or between current management guidelines
4. existing Cochrane systematic reviews concluded there was a lack of evidence for an intervention, but additional evidence is now available or if there was no current Cochrane review.

Secondary criteria were whether:

5. the intervention was already prioritised by healthcare users and healthcare practitioners in the James Lind Alliance Priority Setting Partnership for tinnitus as a 'top 10' treatment uncertainty.
6. there were sufficient new RCTs for a new or updated review to be meaningful.
7. interventions were referred to in the tinnitus research network (TINNET) European clinical practice guideline.
8. there was evidence for variability in clinical practice, within or across countries.

All methodological considerations, and importance to key stakeholders were considered together in prioritising updated and new systematic reviews. For each of the interventions authors judged how many of the primary and secondary criteria were met. From this a list of high priority reviews was formulated.

RESULTS

Summary of existing Cochrane reviews

The Cochrane Library contained 10 existing Cochrane reviews on tinnitus: amplification with hearing aids (Hoare et al., 2014), anticonvulsant drugs (Hoekstra et al., 2011), antidepressant drugs (Baldo et al., 2012), Cognitive Behavioural Therapy (CBT) (Martinez-Devesa et al., 2010), Ginkgo biloba (Hilton et al., 2013), hyperbaric oxygen (for idiopathic sudden

sensorineural hearing loss and tinnitus) (Bennett et al., 2012), repetitive Transcranial Magnetic Stimulation (rTMS) (Meng et al., 2011), sound therapy (masking) (Hobson et al., 2012), Tinnitus Retraining Therapy (TRT) (Phillips and McFerran, 2010a), and zinc supplements (Person et al., 2016). A further eight protocols for systematic reviews had been published. Four were protocols for reviews in progress: CBT (Fuller et al., 2017b), glutamate receptor antagonists (Imsuwansri et al., 2016), melatonin (Ajayi et al., 2014), and neuromodulation (desynchronisation) (Hoare et al., 2015). In the review of TRT (Phillips and McFerran, 2010a), the literature search unearthed a number of studies that purported to be TRT but on inspection did not adhere to the strict protocol described by the developers of TRT (Jastreboff and Hazell, 2004). Many of these studies observed the underlying principles of TRT and its scientific rationale which is generally referred to as the neurophysiological model of tinnitus (Jastreboff, 1990). The authors of the TRT Cochrane review therefore proposed to write a separate review of these studies which they described as modified TRT. After discussion it was decided that a single review of both standard (unmodified) TRT and modified TRT would be more appropriate and a protocol for a review was published (Phillips and McFerran, 2010b). However, progress on this new review was suspended at the suggestion of Cochrane. Methods in this protocol were judged as needing updating.

The other three published protocols (acupuncture (Li et al., 2016), low-level laser therapy (Peng et al., 2014), and an overview of systematic reviews of interventions (Maldonado Fernández et al., 2015) were withdrawn before the reviews were conducted or completed. Eight of the 10 published Cochrane reviews were assessed as having outdated methods by the Cochrane methodologist (EA). The review of zinc supplementation was judged as up-to-date and the methods robust (Person et al., 2016). The review of amplification with hearing aids was judged to have up-to-date methods such that the decision to update would depend on

whether additional RCTs were identified. The number of records included in each of the 10 Cochrane reviews was between one and eight.

New trials for potential inclusion in Cochrane reviews

Scoping searches identified 1080 records (Figure 1). Based on title/abstract screening 731 records were selected for full text screening by at least one author. A further 318 records were excluded that were duplicates (n=127), out of scope (n=11), not randomised (n=86), conference abstracts with no results published (n=70), or required translation for which we did not have the resources (Chinese, Japanese, Swedish, Spanish; n=15). Nine abstracts/full texts were not available. An additional 24 records were identified from lists of references of systematic reviews bringing the total number of records for full text screening and data charting to 437. Among those, 365 records were identified that were new (not covered in existing Cochrane reviews) RCTs with published results: PICOS data were extracted from those records. In addition, 51 unpublished registered randomised trials were identified and data regarding PICOS and trial status were extracted.

*** INSERT FIGURE 1 ABOUT HERE***

Education and information

Eight trials were identified that examined information or education.

Sound-based interventions

Forty-three new trials of sound-based interventions were identified. The interventions trialled included: 1) Amplification only devices (n=8); 2) Sound generator only devices (sometimes referred to as maskers; n=20); 3) Combination devices (i.e. combined amplification and sound generators; n=5); 4) Acoustic Coordinated Reset (CR) Neuromodulation (n=3); 5)

Phase-tailored sound treatment (n=1); 6) Spectrally tailored sound treatment (n=2); and 7) Auditory training (n=4).

Psychology-based interventions

Thirty-nine new trials of psychology-based intervention were identified. Thirty-three of those trialled CBT interventions and three trialled counselling. For the purpose of this scoping review we included all studies using cognitive and/or behavioural approaches to treatment. It is worth noting that there is a published protocol for a revision of the Cochrane review of CBT for tinnitus (Fuller et al., 2017a). This review will examine all interventions for tinnitus that include cognitive, and/or behavioural interventions. Those would include Acceptance and Commitment Therapy (ACT) and Mindfulness-based therapies, described as different 'waves' of CBT.

Self-help interventions

One trial was identified that examined a self-help intervention, namely an online discussion forum.

Relaxation therapy

Eighteen trials of relaxation therapy were identified including: Neurofeedback/Biofeedback (n=8); Hypnosis/Hypnotherapy (n=3); 3) Relaxation (n=7).

Pharmacology-based interventions

One hundred and fifty-eight new trials of pharmacological interventions for tinnitus were identified. They were classified in nine different categories based on the WHO ATC system: 1) Alimentary tract and metabolism (n=12); 2) Blood and blood forming organs (n=8); 3) Cardiovascular system (n=20); 4) Genito-urinary system and sex hormones (n=5); 5) Musculo-skeletal system (n=3); 6) Nervous system (n=83); 7) Respiratory system (n=1); 8)

Systemic hormonal preparations, excluding sex hormones and insulins (n=8); and 9) Various (n=2). Thirteen trials of non-classified (i.e. experimental) medications were also identified.

Manual physical therapy

Five trials of manual physical therapy were identified including: 1) Cervical spine treatment (n=3); 2) Myofascial trigger point deactivation (n=1); and 3) Temporomandibular Joint Treatment (n=1).

Magnetic stimulation

Forty-one trials of magnetic stimulation were identified: 1) Repetitive Transcranial Magnetic Stimulation (rTMS, n=36), 2) Continuous Theta Burst Stimulation (cTBS, n=2); 3) Deep Transcranial Magnetic Stimulation (n=1); 4) Electromagnetic Ear Stimulation (n=1); and 5) Rare-earth magnets placed close to the tympanic membrane (n=1).

Electrical stimulation

Twenty-three new trials of electrical stimulation were identified including: 1) Cochlear implant (n=3); 2) Transcranial Alternating Current Stimulation (tACS; n=1); 3) Transcranial Direct Current Stimulation (tDCS; n=11); 4) Vagus Nerve Stimulation (VNS; n=3); 5) Transcutaneous Electrical Nerve Stimulation (TENS; n=2); 6) Ear electrical stimulation via surface tympanic electrode (n=1); and 7) External electrical stimulation via mastoid bones (n=1). According to the published Cochrane protocol of neuromodulation (desynchronisation) for tinnitus (Hoare et al., 2015), all trials of electrical stimulation for tinnitus are likely to be included.

Complementary and alternative therapies

Fifty-six trials of complementary and alternative therapies were identified including: 1) Acupuncture (n=26); 2) Dietary supplements and herbal remedies (n=10); 3) Laser treatment

(n=14); 4) Ozone (n=1); 5) Ultrasound (n=2); 6) Vibratory stimulation (n=2); and 7) Virtual reality (n=1).

Complex interventions

Twenty-four trials of complex interventions were identified including: 1) Heidelberg Neuro-Music Therapy (n=2); 2) Perceptual/cognitive training (n=4); 3) Progressive Tinnitus Management (PTM, n=4); 4) Tinnitus Retraining Therapy (TRT, including modified TRT; n=9); 5) Combination of psychological approaches with other management strategies (n=3); 6) bimodal treatment involving TRT with EMDR and TRT with CBT (n=1); and 7) a combination of sound based, educational and integrated medicine therapies (n=1).

Priority reviews on tinnitus

Three high priority reviews were identified based on the pre-defined priority criteria. Those were: 1) sound therapy using amplification devices and/or sound generators for tinnitus; 2) betahistine; 3) CBT.

Sound therapy met the first three primary priority criteria, the existing Cochrane reviews concluded a lack of evidence of clinical effectiveness (Hoare et al., 2014a, Hobson et al., 2012) and new trials were identified. Our recommendation was that a priority Cochrane review should include amplification only devices, combination devices (combined amplification and sound generation), and sound generators. Suggested comparisons for inclusion were: 1) Amplification only vs waiting-list control, placebo, education/information only with no device; 2) Combination devices vs waiting-list control, placebo, education/information only with no device, amplification only, sound generator only; 3) Sound generator only vs waiting-list control, placebo, education/information only with no device. Trials that have conditions that explicitly included counselling (such as TRT, PTM, Neuromonics) should be excluded. Counselling was defined according to Culley and Bond

(2011) as a process that aims to empower patients to reach decisions and take actions for themselves. Establishing a therapeutic relationship, clarifying and defining problems, planning actions, and managing expectations are all key features of the approach. Education and information giving can be entirely one-way, whereas counselling is about empowerment and enabling patients to arrive at their own solutions using their own internal resources. Therefore, unless there were explicit efforts and description of a process towards empowerment in trial reports, and a trained therapist delivered it, then it was not considered counselling.Betahistine also met the first three primary priority criteria and there is no existing Cochrane review. We identified six trials for consideration. Comparisons should include placebo, no intervention, education and information only. However, it should be noted that only three trials include the above comparisons (n=3) and the others would not be suitable for synthesis. Subgroup analyses with and without Ménière's disease should also be considered, but we note that there is an existing Cochrane review on Betahistine for Ménière's disease or syndrome which has impact on tinnitus symptom severity as a secondary outcome (Van Esch et al., 2018).

CBT met the first three primary priority criteria. Although there is an existing Cochrane review (Martinez-Devesa et al., 2010) it is now outdated and does not include all cognitive, and/or behavioural interventions (Acceptance and Commitment Therapy (ACT) and Mindfulness-based therapies, described as different 'waves' of CBT). A Cochrane review examining all cognitive and behavioural approaches for tinnitus is currently ongoing (Fuller et al., 2017b).

Further priorities (meeting fewer priority criteria) included: 1) Gingko biloba; 2) anxiolytics; 3) hypnotics; 4) antiepileptics; 5) neuromodulation.

Gingko biloba met the first two primary priority criteria. The existing Cochrane review concluded a lack of evidence for effectiveness (Hilton et al., 2013) and new trials were identified. Suggested comparisons include placebo, no intervention, education and information only. Anxiolytics met the first two primary criteria and there is no existing Cochrane review. Nine trials have been identified which may be eligible. Suggested comparisons are placebo, no intervention, education and information only. Hypnotics meets the first two primary criteria and there is no existing Cochrane review. Eight trials have been identified which may be eligible for inclusion. Suggested comparisons are placebo, no intervention, education and information only. Antiepileptics met the first two primary criteria and there is no existing Cochrane review. Eleven trials have been identified. Suggested comparisons include placebo, no intervention, education and information only. Neuromodulation met two primary criteria including being in scope of the NICE guidelines. However, a Cochrane review of neuromodulation for tinnitus is currently ongoing (Hoare et al., 2015).

CONCLUSIONS

This technical report highlights a comprehensive exercise we undertook to prioritise topics of unmet need for high-quality systematic review in tinnitus management.

Importantly, these priority reviews will respond to unanswered questions identified in current and developing clinical practice guidelines for tinnitus. Three high priority reviews are recommended: 1) sound therapy using amplification devices and/or sound generators for tinnitus; 2) betahistine; 3) Cognitive Behaviour Therapy. Further priorities are: 4) Gingko biloba; 5) anxiolytics; 6) hypnotics; 7) antiepileptics; 8) neuromodulation.

Applying a prioritisation process ensures that resources are invested most effectively in work that meets the needs of funders and stakeholders and addresses known discrepancies or gaps in clinical knowledge. This particular prioritisation work focused on UK clinical practice for tinnitus and therefore the relevant priority criteria, such as availability of the intervention within the NHS and inclusion in the scope of the NICE tinnitus guideline. However, the process can easily be adapted to a range of international, national or local settings and priorities. For example, regional or country-specific clinical practice can be taken into consideration as well as guidelines at the national, regional or international level (e.g. European or country-specific) when formulating the priority criteria.

The scoping exercise described here has already resulted in the expedited production of two Cochrane systematic reviews (Sereda et al., 2018; Wegner et al., 2018) in part to inform the NICE guideline on tinnitus which is currently under development. A further three priority reviews are currently in progress (Fuller et al., 2017b; Hoare et al. 2015; and Gingko biloba – protocol in preparation).

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FIGURE LEGEND

Figure 1. Flow diagram illustrating search strategy and scoping review stages

SUPPLEMENTAL MATERIAL

Supplemental material 1. Summary of priority criteria for each of the interventions

ABSTRACT

Objective: To develop an innovative prioritisation process to identify topics for new or updated systematic reviews of tinnitus ~~and hearing~~ research.

Design: A two stage prioritisation process was devised. Firstly, a scoping review assessed the amount of randomised-controlled-trial-level evidence available. This enabled development of selection criteria for future reviews, aided the design of template protocol, and suggested the scale of work that would be required to conduct these reviews. Secondly, using the pre-defined primary and secondary criteria, interventions were prioritised for systematic review.

Study sample: Searches identified 1080 records. After removal of duplicates and out of scope works, 437 records remained for full data charting.

Results: The process was tested, using subjective tinnitus as the clinical condition and using Cochrane as the systematic review platform. The criteria produced by this process identified three high priority reviews: 1) Sound therapy using amplification devices and/or sound generators; 2) Betahistine, and 3) Cognitive Behaviour Therapy. Further secondary priorities were: 4) Gingko biloba, 5) Anxiolytics, 6) Hypnotics, 7) Antiepileptics, and 8) Neuromodulation.

Conclusions: A process was developed which successfully identified priority areas for Cochrane systematic reviews of interventions for subjective tinnitus. This technique could easily be transferred to other conditions and other types of systematic reviews.

Keywords: Cochrane, systematic review, priority, management, treatment, tinnitus

INTRODUCTION

Systematic reviews and meta-analyses represent the highest level of evidence for the effectiveness of clinical interventions and hold a critical place in informing health policy and evidence-based practice (Greenwell et al.2016; Morata et al., 2017). One of the foremost organisations producing systematic reviews is Cochrane, which is a UK based charity (not-for-profit organisation) that supervises a global independent network of healthcare practitioners, researchers, patient advocates and others. It represents more than 11,000 members and over 68,000 supporters from over 130 countries (https://www.cochrane.org/about-us). Cochrane authors conduct systematic reviews of health-care interventions and diagnostic tests which are published as Cochrane Reviews in the Cochrane Library. Previously, Cochrane authors self-selected topics for their reviews and submitted proposals to Cochrane for approval. This process has been updated and now, Cochrane groups are encouraged to work strategically to respond to the needs of funders and key stakeholders to produce reviews on topics of the highest priority to users. One approach to prioritising these reviews is to conduct a scoping exercise (https://ent.cochrane.org/our-evidence/prioritisation/scoping-projects). Cochrane Ear, Nose, & Throat Disorders (Cochrane ENT) group this has developed suites of reviews with an "optimal, shared protocol with a well-designed and consistent set of outcome measures" (Cochrane ENT Group, 2019).

In this report we describe a comprehensive exercise used to prioritise systematic reviews of interventions for tinnitus conducted for the Cochrane ENT group.

Subjective tinnitus is described as the perception of sound in the absence of an external sound source (Jastreboff and Hazell, 2004). It is a symptom experienced by 10-30% of the adult population (McCormack et al., 2016). About 20% of people with tinnitus experience it as

bothersome ~~and negatively affecting quality of life~~ (McCormack et al., 2016). Problems associated with tinnitus include sleep disturbances, hearing difficulties, difficulties with concentration, social isolation, anxiety, depression, and emotional difficulties such as irritation or stress (Davis and El Refaie, 2000). It is estimated that the prevalence of tinnitus in those adults seeking medical help for hearing problems is as high as 85% (Axelsson and Ringdahl, 1989; Davis and El Refaie, 2000; Meikle and Taylor-Walsh, 1984).

Tinnitus represents a major financial burden to the healthcare system. For example, in England there are approximately 0.75 million primary care consultations each year where the primary complaint is tinnitus (El-Shunnar et al., 2011) and the average cost to the National Health System of tinnitus treatment per year is estimated to be GB£750M. The estimated annual societal costs of tinnitus in the UK is GB£2.7 billion (Stockdale et al., 2017).

There is currently no gold standard treatment for tinnitus, rather, various management strategies are used or have been trialled. Those include education and information, sound-based interventions, psychology-based interventions, self-help interventions, relaxation therapy, pharmacology-based interventions, manual physical therapy, magnetic stimulation, electrical stimulation, complementary and alternative therapies, and combination of two or more approaches (complex interventions). Guidelines for the management of tinnitus have been developed in the USA and Europe (Cima et al., 2019; Fuller et al., 2017a). In the UK, there are commissioning guidelines for tinnitus services for adults (Department of Health, 2009), and clinical practice guidance for the assessment and management of tinnitus in children (British Society of Audiology, 2015) A Clinical Knowledge Summary has been produced by the National Institute for Health and Care Excellence (NICE) and two national guidelines are in development: the first by NICE; the second by the British Society of Audiology (BSA). NICE has published the scope of the guidelines that are in development (https://www.nice.org.uk/guidance/gid-ng10077/documents/final-scope) outlining which

factors will and will not be considered by the guidelines. Effective guidelines can only be developed if there is strong evidence-based information available. If such high-level evidence is not available, recommendations arising from the guidelines are weak and clinically ineffective. These are just some of the drivers for prioritising new and updating existing Cochrane systematic reviews of interventions for tinnitus.

METHODS

The prioritisation process was conducted in two stages. First, a scoping review was conducted to estimate the volume of randomised controlled trial (RCT) level evidence available, to facilitate prioritisation, to aid in the design of a template protocol, and to estimate the work involved in conducting a suite of priority reviews. Secondly, interventions were prioritised for review according to a set of pre-defined criteria.

Scoping review

We followed the methodological framework of Arksey and O'Malley (2005). This consisted of: (1) identifying potentially relevant records; (2) selecting relevant records; (3) extracting data items; and (4) collating, summarising, and reporting the results. The PRISMA-ScR checklist (Tricco et al., 2018) guided reporting of the methods and results of the scoping review.

Search strategy

In July 2017 we conducted a search of the Cochrane ENT Trials Register (via the Cochrane Register of studies) for RCTs. There were no language, publication year, or publication status restrictions. The search was run in the Cochrane ENT Register

(https://ent.cochrane.org/resources/searching-studies/cochrane-ent-trials-register) using the following strategy:

1 MESH DESCRIPTOR Tinnitus EXPLODE ALL AND INREGISTER

2 tinnit* AND INREGISTER

3 #1 OR #2 AND INREGISTER,

where MESH DESCRIPTOR – Medical Subject Headings: The National Library of Medicine controlled vocabulary thesaurus, INREGISTER – in the Cochrane ENT register, EXPLODE ALL – search for selected subject heading (Tinnitus) and all of the subject headings in its family.

The Cochrane ENT Register is populated using the methods described on the Cochrane ENT website (https://ent.cochrane.org/resources/searching-studies/cochrane-ent-trials-register).

We also searched the Cochrane database of Systematic Reviews for all published reviews and protocols for Cochrane reviews with 'tinnitus' in the title.

Selection of studies

Three authors (MS, DJH, DAH) independently screened all abstracts to determine eligibility for inclusion in the scoping review. Records were carried forward for full screening if at least one of the authors selected it. We considered multiple articles reporting the same trial together as a single record. Disagreements were discussed between authors until a consensus was reached. Records were considered for inclusion according to PICOS (Methley et al., 2014), as follows:

***P**opulation:* Children and/or adults with subjective tinnitus

***I**ntervention:* All interventions for subjective tinnitus

***C**omparator:* No intervention (e.g. waiting list), different intervention, placebo

Outcome: Did not form an inclusion criterion

Study design: Randomised controlled trials only.

Data extraction

Data were extracted using a bespoke template form designed by the authors (MS and DJH), piloted on a subset of records, and revised before formal data extraction was undertaken. PICOS data were extracted (population, intervention, comparator, outcomes, and outcome measures used, and study design). Two authors independently extracted the data.

For each intervention, we recorded whether there were existing RCTs, the number of RCTs, and whether those RCTs were included or not in existing Cochrane reviews. In scoping the literature, drug trials were catalogued (by DMcF) according to the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical (ATC) Classification System (https://www.whocc.no/atc_ddd_index/).

Methodological assessment of published Cochrane reviews

A list of published Cochrane systematic reviews and published Cochrane protocols was populated. When judging whether an existing Cochrane systematic review required updating or replacing, we considered the date of the most recent literature search of the review, and whether ongoing studies were identified in those reviews. Both of these factors were used to consider whether there was new research that may alter the estimates of effect, the quality of the overall evidence, or the conclusions drawn in the published review. Other methodological aspects of the systematic reviews were assessed including (1) whether a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram was included; (2) whether the latest risk of bias tool was used; (3) whether a 'Summary of Findings (SoF)' table was included; (4) whether the 'Grading of Recommendations, Assessment,

Development and Evaluation' (GRADE; https://gradepro.org/) tool was used (Schünemann et al., 2013); (5) whether the assessed outcomes included measures of benefits and harms of the intervention; and (6) whether the review included all of the methods sections currently recommended by Cochrane (Higgins and Green, 2011).

Prioritisation process

Authors of this scoping review were experts in tinnitus (clinical researchers, a psychologist, ENT surgeon, and an audiologist) or experts in Cochrane systematic review methodology.~~Authors of this scoping review were experts in tinnitus, clinical researchers, a psychologist, ENT surgeon, and an audiologist or experts in Cochrane systematic review methodology.~~ All authors took part in agreeing the criteria that were used to prioritise reviews. Firstly a list of criteria was populated including criteria formulated according to the remit from National Institute for Health Research (NIHR) with additional criteria proposed by individual authors. Secondly authors ranked these criteria in order of importance. Based on the ranking, four primary and four secondary criteria were formulated.

Primary criteria were whether:

1. the intervention ~~is~~ was available for tinnitus management within the National Health Service (NHS) When considering drug treatments for tinnitus, this included drugs that ~~are~~ were used on-licence such as betahistine for Ménière's disease-associated tinnitus. It also included drugs used that have been recorded as being used off-licence as a primary tinnitus treatment (Langguth et al., 2009; Hall et al., 2011; McFerran et al., 2018). It did not include drugs used primarily for treating comorbid conditions.
2. the intervention ~~is~~ was included in the NICE document, *Guidelines scope. Tinnitus: assessment and management.* (https://www.nice.org.uk/guidance/gid-

ng10077/documents/final-scope). This document ~~outlines~~ outlined the proposed contents of the forthcoming NICE Guideline.

3. there was 'no recommendation' or disagreement in recommendations for an intervention within or between current management guidelines
4. existing Cochrane systematic reviews concluded there was a lack of evidence for an intervention, but additional evidence is now available or if there was~~is~~ no current Cochrane review.

Secondary criteria were whether:

5. the intervention ~~had~~ was already ~~been~~ prioritised by healthcare users and healthcare practitioners in the James Lind Alliance Priority Setting Partnership for tinnitus as a 'top 10' treatment uncertainty.
6. there were sufficient new RCTs for a new or updated review to be meaningful.
7. interventions were referred to in the tinnitus research network (TINNET) European clinical practice guideline.
8. there was evidence for variability in clinical practice, within or across countries.

All methodological considerations, and importance to key stakeholders were considered together in prioritising updated and new systematic reviews. For each of the interventions authors judged how many of the primary and secondary criteria were met. From this a list of high priority reviews was formulated.

RESULTS

Summary of existing Cochrane reviews

The Cochrane Library contained 10 existing Cochrane reviews on tinnitus: amplification with hearing aids (Hoare et al., 2014), anticonvulsant drugs (Hoekstra et al., 2011), antidepressant

drugs (Baldo et al., 2012), Cognitive Behavioural Therapy (CBT) (Martinez-Devesa et al., 2010), Ginkgo biloba (Hilton et al., 2013), hyperbaric oxygen (for idiopathic sudden sensorineural hearing loss and tinnitus) (Bennett et al., 2012), repetitive Transcranial Magnetic Stimulation (rTMS) (Meng et al., 2011), sound therapy (masking) (Hobson et al., 2012), Tinnitus Retraining Therapy (TRT) (Phillips and McFerran, 2010a), and zinc supplements (Person et al., 2016). A further eight protocols for systematic reviews had been published. Four were protocols for reviews in progress: CBT (Fuller et al., 2017b), glutamate receptor antagonists (Imsuwansri et al., 2016), melatonin (Ajayi et al., 2014), and neuromodulation (desynchronisation) (Hoare et al., 2015). In the review of TRT (Phillips and McFerran, 2010a), the literature search unearthed a number of studies that purported to be TRT but on inspection did not adhere to the strict protocol described by the developers of TRT (Jastreboff and Hazell, 2004). Many of these studies observed the underlying principles of TRT and its scientific rationale which is generally referred to as the neurophysiological model of tinnitus (Jastreboff, 1990). The authors of the TRT Cochrane review therefore proposed to write a separate review of these studies which they described as modified TRT. After discussion it was decided that a single review of both standard (unmodified) TRT and modified TRT would be more appropriate and a protocol for a review was published (Phillips and McFerran, 2010b). However, progress on this new review was suspended at the suggestion of Cochrane. Methods in this protocol were judged as needing updating. The other three published protocols (acupuncture (Li et al., 2016), low-level laser therapy (Peng et al., 2014), and an overview of systematic reviews of interventions (Maldonado Fernández et al., 2015)) were withdrawn before the reviews were conducted or completed.~~There were 10 existing Cochrane reviews on tinnitus (Baldo et al., 2012; Bennett et al., 2012; Hilton et al., 2013; Hoare et al., 2014; Hobson et al., 2012; Hoekstra et al., 2011; Martinez-Devesa et al., 2010; Meng et al., 2011; Person et al., 2016; Phillips and McFerran, 2010a) published in The~~

~~Cochrane Library. The interventions evaluated were Tinnitus Retraining Therapy (TRT), Cognitive Behavioural Therapy (CBT), anticonvulsants, repetitive Transcranial Magnetic Stimulation (rTMS), antidepressants, sound therapy (masking), Ginkgo biloba, hyperbaric oxygen (for idiopathic sudden sensorineural hearing loss and tinnitus), zinc supplements, and amplification with hearing aids. A further eight protocols for systematic reviews had been published. Five were protocols for reviews in progress, on neuromodulation (desynchronisation) (Hoare et al., 2015), neurophysiological model-based treatments (Phillips and McFerran, 2010b), CBT (Fuller et al., 2017b), glutamate receptor antagonists (Imsuwansri et al., 2016), and melatonin (Ajayi et al., 2014). The other three published protocols (acupuncture, low-level laser therapy, and an overview of systematic reviews of interventions) were withdrawn before the reviews were conducted or completed (Li et al., 2016; Maldonado Fernández et al., 2015; Peng et al., 2014). The protocol for neurophysiological-based treatments for tinnitus (Phillips and McFerran, 2010b) planned to include unmodified and modified TRT, meaning it would constitute an update to the TRT review. However, progress on this new review has been suspended at the suggestion of Cochrane. Methods in this protocol were judged as needing updating.~~

Eight of the 10 published Cochrane reviews were assessed as having outdated methods by the Cochrane methodologist (EA). The review of zinc supplementation was judged as up-to-date and the methods robust (Person et al., 2016). The review of amplification with hearing aids was judged to have up-to-date methods such that the decision to update would depend on whether additional RCTs were identified. The number of records included in each of the 10 Cochrane reviews was between one and eight.

New trials for potential inclusion in Cochrane reviews

Scoping searches identified 1080 records (Figure 1). Based on title/abstract screening 731 records were selected for full text screening by at least one author. A further 318 records were excluded that were duplicates (n=127), out of scope (n=11), not randomised (n=86), conference abstracts with no results published (n=70), or required translation for which we did not have the resources (Chinese, Japanese, Swedish, Spanish; n=15). Nine abstracts/full texts were not available. An additional 24 records were identified from lists of references of systematic reviews bringing the total number of records for full text screening and data charting to 437. Among those, 365 records were identified that were new (not covered in existing Cochrane reviews) RCTs with published results: PICOS data were extracted from those records. In addition, 51 unpublished registered randomised trials were identified and data regarding PICOS and trial status were extracted.

*** INSERT FIGURE 1 ABOUT HERE***

Education and information

Eight trials were identified that examined information or education.

Sound-based interventions

Forty-three new trials of sound-based interventions were identified. The interventions trialled included: 1) Amplification only devices (n=8); 2) Sound generator only devices (sometimes referred to as maskers; n=20); 3) Combination devices (i.e. combined amplification and sound generators; n=5); 4) Acoustic Coordinated Reset (CR) Neuromodulation (n=3); 5) Phase-tailored sound treatment (n=1); 6) Spectrally tailored sound treatment (n=2); and 7) Auditory training (n=4).

Psychology-based interventions

Thirty-nine new trials of psychology-based intervention were identified. Thirty-three of those trialled CBT interventions and three trialled counselling. For the purpose of this scoping review we included all studies using cognitive and/or behavioural approaches to treatment. It is worth noting that there is a published protocol for a revision of the Cochrane review of CBT for tinnitus (Fuller et al., 2017a). This review will examine all interventions for tinnitus that include cognitive, and/or behavioural interventions. Those would include Acceptance and Commitment Therapy (ACT) and Mindfulness-based therapies, described as different 'waves' of CBT.

Self-help interventions

One trial was identified that examined a self-help intervention, namely an online discussion forum.

Relaxation therapy

Eighteen trials of relaxation therapy were identified including: Neurofeedback/Biofeedback (n=8); Hypnosis/Hypnotherapy (n=3); 3) Relaxation (n=7).

Pharmacology-based interventions

One hundred and fifty-eight new trials of pharmacological interventions for tinnitus were identified. They were classified in nine different categories based on the WHO ATC system: 1) Alimentary tract and metabolism (n=12); 2) Blood and blood forming organs (n=8); 3) Cardiovascular system (n=20); 4) Genito-urinary system and sex hormones (n=5); 5) Musculo-skeletal system (n=3); 6) Nervous system (n=83); 7) Respiratory system (n=1); 8) Systemic hormonal preparations, excluding sex hormones and insulins (n=8); and 9) Various (n=2). Thirteen trials of non-classified (i.e. experimental) medications were also identified.

Manual physical therapy

Five trials of manual physical therapy were identified including: 1) Cervical spine treatment (n=3); 2) Myofascial trigger point deactivation (n=1); and 3) Temporomandibular Joint Treatment (n=1).

Magnetic stimulation

Forty-one trials of magnetic stimulation were identified: 1) Repetitive Transcranial Magnetic Stimulation (rTMS, n=36), 2) Continuous Theta Burst Stimulation (cTBS, n=2); 3) Deep Transcranial Magnetic Stimulation (n=1); 4) Electromagnetic Ear Stimulation (n=1); and 5) Rare-earth magnets placed close to the tympanic membrane (n=1).

Electrical stimulation

Twenty-three new trials of electrical stimulation were identified including: 1) Cochlear implant (n=3); 2) Transcranial Alternating Current Stimulation (tACS; n=1); 3) Transcranial Direct Current Stimulation (tDCS; n=11); 4) Vagus Nerve Stimulation (VNS; n=3); 5) Transcutaneous Electrical Nerve Stimulation (TENS; n=2); 6) Ear electrical stimulation via surface tympanic electrode (n=1); and 7) External electrical stimulation via mastoid bones (n=1). According to the published Cochrane protocol of neuromodulation (desynchronisation) for tinnitus (Hoare et al., 2015), all trials of electrical stimulation for tinnitus are likely to be included.

Complementary and alternative therapies

Fifty-six trials of complementary and alternative therapies were identified including: 1) Acupuncture (n=26); 2) Dietary supplements and herbal remedies (n=10); 3) Laser treatment (n=14); 4) Ozone (n=1); 5) Ultrasound (n=2); 6) Vibratory stimulation (n=2); and 7) Virtual reality (n=1).

Complex interventions

Twenty-four trials of complex interventions were identified including: 1) Heidelberg Neuro-Music Therapy (n=2); 2) Perceptual/cognitive training (n=4); 3) Progressive Tinnitus Management (PTM, n=4); 4) Tinnitus Retraining Therapy (TRT, including modified TRT; n=9); 5) Combination of psychological approaches with other management strategies (n=3); 6) bimodal treatment involving TRT with EMDR and TRT with CBT (n=1); and 7) a combination of sound based, educational and integrated medicine therapies (n=1).

Priority reviews on tinnitus

Three high priority reviews were identified based on the pre-defined priority criteria. Those were: 1) sound therapy using amplification devices and/or sound generators for tinnitus; 2) betahistine; 3) CBT.

Sound therapy met the first three primary priority criteria, the existing Cochrane reviews concluded a lack of evidence of clinical effectiveness (Hoare et al., 2014a, Hobson et al., 2012) and new trials were identified. Our recommendation was that a priority Cochrane review should include amplification only devices, combination devices (combined amplification and sound generation), and sound generators. Suggested comparisons for inclusion were: 1) Amplification only vs waiting-list control, placebo, education/information only with no device; 2) Combination devices vs waiting-list control, placebo, education/information only with no device, amplification only, sound generator only; 3) Sound generator only vs waiting-list control, placebo, education/information only with no device. Trials that have conditions that explicitly included counselling (such as TRT, PTM, Neuromonics) should be excluded. Counselling was defined according to Culley and Bond (2011) as a process that aims to empower patients to reach decisions and take actions for themselves. Establishing a therapeutic relationship, clarifying and defining problems, planning actions, and managing expectations are all key features of the approach. Education

and information giving can be entirely one-way, whereas counselling is about empowerment and enabling patients to arrive at their own solutions using their own internal resources. Therefore, unless there were explicit efforts and description of a process towards empowerment in trial reports, and a trained therapist delivered it, then it was not considered counselling.

Betahistine also met the first three primary priority criteria and there is no existing Cochrane review. We identified six trials for consideration. Comparisons should include placebo, no intervention, education and information only. However, it should be noted that only three trials include the above comparisons (n=3) and the others would not be suitable for synthesis. Subgroup analyses with and without Ménière's disease should also be considered, but we note that there is an existing Cochrane review on Betahistine for Ménière's disease or syndrome which has impact on tinnitus symptom severity as a secondary outcome (Van Esch et al., 2018).

CBT met the first three primary priority criteria. Although there is an existing Cochrane review (Martinez-Devesa et al., 2010) it is now outdated and does not include all cognitive, and/or behavioural interventions (Acceptance and Commitment Therapy (ACT) and Mindfulness-based therapies, described as different 'waves' of CBT). A Cochrane review examining all cognitive and behavioural approaches for tinnitus is currently ongoing (Fuller et al., 2017b).

Further priorities (meeting fewer priority criteria) included: 1) Gingko biloba; 2) anxiolytics; 3) hypnotics; 4) antiepileptics; 5) neuromodulation.

Gingko biloba met the first two primary priority criteria. The existing Cochrane review concluded a lack of evidence for effectiveness (Hilton et al., 2013) and new trials were identified. Suggested comparisons include placebo, no intervention, education and

information only. Anxiolytics met the first two primary criteria and there is no existing Cochrane review. Nine trials have been identified which may be eligible. Suggested comparisons are placebo, no intervention, education and information only. Hypnotics meets the first two primary criteria and there is no existing Cochrane review. Eight trials have been identified which may be eligible for inclusion. Suggested comparisons are placebo, no intervention, education and information only. Antiepileptics met the first two primary criteria and there is no existing Cochrane review. Eleven trials have been identified. Suggested comparisons include placebo, no intervention, education and information only. Neuromodulation met two primary criteria including being in scope of the NICE guidelines. However, a Cochrane review of neuromodulation for tinnitus is currently ongoing (Hoare et al., 2015).

CONCLUSIONS

This technical report highlights a comprehensive exercise we undertook to prioritise topics of unmet need for high-quality systematic review in tinnitus management.

Importantly, these priority reviews will respond to unanswered questions identified in current and developing clinical practice guidelines for tinnitus. Three high priority reviews are recommended: 1) sound therapy using amplification devices and/or sound generators for tinnitus; 2) betahistine; 3) Cognitive Behaviour Therapy. Further priorities are: 4) Gingko biloba; 5) anxiolytics; 6) hypnotics; 7) antiepileptics; 8) neuromodulation.

Applying a prioritisation process ensures that resources are invested most effectively in work that meets the needs of funders and stakeholders and addresses known discrepancies or gaps in clinical knowledge. This particular prioritisation work focused on UK clinical practice for

tinnitus and therefore the relevant priority criteria, such as availability of the intervention within the NHS and inclusion in the scope of the NICE tinnitus guideline. However, the process can easily be adapted to a range of international, national or local settings and priorities. For example, regional or country-specific clinical practice can be taken into consideration as well as guidelines at the national, regional or international level (e.g. European or country-specific) when formulating the priority criteria.

The scoping exercise described here has already resulted in the expedited production of two Cochrane systematic reviews (Sereda et al., 2018; Wegner et al., 2018) in part to inform the NICE guideline on tinnitus which is currently under development. A further three priority reviews are currently in progress (Fuller et al., 2017b; Hoare et al. 2015; and Gingko biloba – protocol in preparation).

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FIGURE LEGEND

Figure 1. Flow diagram illustrating search strategy and scoping review stages

SUPPLEMENTAL MATERIAL

Supplemental material 1. Summary of priority criteria for each of the interventions

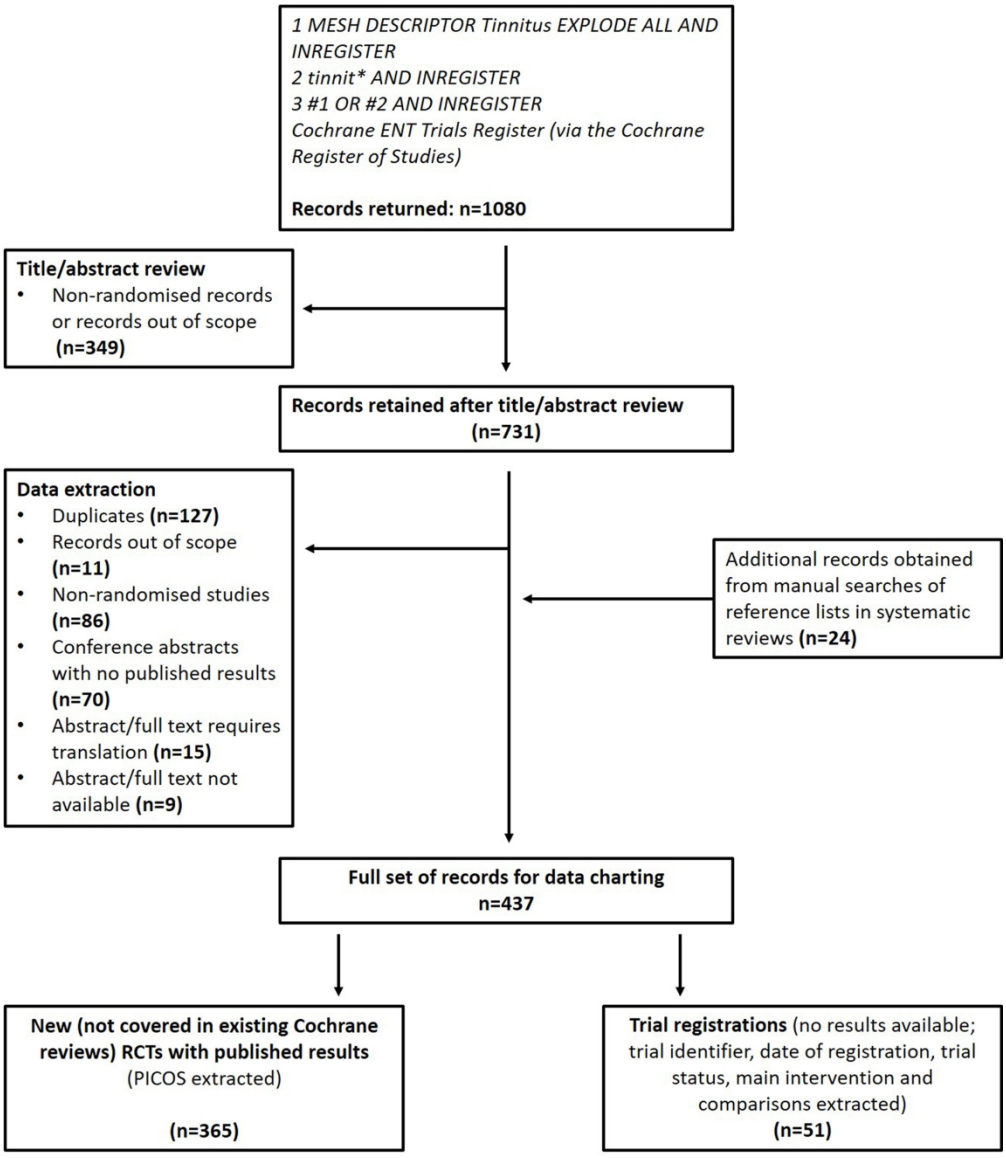

Figure 1. Flow diagram illustrating search strategy and scoping review stages

177x205mm (600 x 600 DPI)

Supplemental material 1: Summary of priority criteria for each of the interventions

Summary of interventions with ratings according to the primary and secondary criteria for prioritisation. To aid prioritisation decisions, four primary criteria were considered: 1. Whether the intervention is available for tinnitus management within the NHS; 2. Whether the intervention is within the scope of the NICE tinnitus guidelines that are currently in development; 3. Whether there was 'no recommendation' or disagreement in recommendations across current management guidelines; and 4. Whether existing Cochrane systematic reviews concluded there was a lack of evidence, but new RCTs are now available or there is no Cochrane review.

In addition, four secondary criteria considered: 5. Whether the intervention has been prioritised in the James Lind Alliance Priority Setting Partnership for tinnitus as a 'top 10' uncertainty; 6. The number of new RCTS identified; 7. Whether interventions are referred to in the TINNET European clinical practice guideline; and 8. Whether there is evidence for variability in clinical practice, within or across countries.

	Primary criteria				**Secondary criteria**			
Intervention	1. NHS	2. NICE	3. Guidelines	4. Cochrane needed	5. JLA	6. New RCTs	7. TINNET	8. Variability
Pharmacological approaches - Alimentary tract and metabolism								
Drugs for functional gastrointestinal disorders	NO	NO	YES	YES	YES	4	NO	YES
Antiemetics and antinauseants	YES	NO	YES	YES	YES	1	NO	YES
Vitamins – Ascorbic acid (Vitamin C)	NO	NO	YES	YES	YES	1	YES	YES
Vitamins – other plain Vitamin preparations	NO	NO	YES	YES	YES	2	YES	YES
Vitamins – Vitamin B-complex, including combinations	NO	NO	YES	YES	YES	2	YES	YES
Mineral supplements – Zinc	NO	NO	YES	NO	YES	0	YES	YES
Mineral supplements – Magnesium	NO	NO	YES	YES	YES	1	YES	YES
Pharmacological approaches - Blood and blood forming organs								

Antithrombotic agents	YES	NO	YES	YES	YES	5	NO	YES
Antianemic preparations	NO	NO	YES	YES	YES	2	YES Vitamin B12	YES
Pharmacological approaches - Cardiovascular system								
Antiarrhytmics	YES	NO	YES	YES	YES	11	NO	YES
Peripheral vasodilators	YES	NO	YES	YES	YES	5	NO	YES
Lipid modifying agents	NO	NO	YES	YES	YES	1	NO	YES
Other cardiac preparations	YES	NO	YES	YES	YES	3	NO	YES
Pharmacological approaches - Genito-urinary system and sex hormones								
Uterotonics	NO	NO	YES	YES	YES	3	NO	YES
Urologicals	NO	NO	YES	YES	YES	2	NO	YES
Pharmacological approaches - Musculo-skeletal system								
Anti-inflammatory and antirheumatic products	YES	NO	YES	YES	YES	1	NO	YES
Muscle relaxants	NO	NO	YES	YES	YES	1	NO	YES
Pharmacological approaches – Nervous system								
Anesthetics - General anesthetics	NO	NO	YES	YES	YES	4	NO	YES
Anesthetics - Local anesthetics	YES	NO	YES	YES	YES	18	NO	YES
Antiepileptics	YES	NO	YES	YES	YES	11	YES Benzo-diazepines	YES
Anti-Parkinson drugs	YES	NO	YES	YES	YES	2	NO	YES

Psycholeptics - Antipsychotics	YES	NO	YES	YES	YES	2	NO	YES
Psycholeptics - Anxiolytics	YES	NO	YES	YES	YES	8	NO	YES
Hypnotics and sedatives	YES	NO	YES	YES Melatonin	YES	8	YES Melatonin	YES
Psychoanaleptics - Antidepressants	YES	NO	YES	YES	YES	4	YES	YES
Psychostimulants and nootropics	YES	NO	YES	YES	YES	1	NO	YES
Anti-dementia drugs	YES	NO Ginkgo biloba	YES	YES	YES	6	YES	YES
Other nervous system drugs – Drugs used in addictive disorders	NO	NO	YES	YES	YES	3	NO	YES
Antivertigo preparations	YES	YES Betahistine	YES	YES	YES	11	NO	YES
Combinations of medications	NO	NO	YES	YES	YES	1	NO	YES
Pharmacological approaches – respiratory system								
Respiratory stimulants	YES	NO	YES	YES	YES	1	NO	YES
Pharmacological approaches - Systemic hormonal preparations, excluding sex hormones and insulins								
Pituitary and hypothalamic hormones and analogues	NO	NO	YES	YES	YES	1	NO	YES
Corticosteroids for systemic use	YES	NO	YES	YES	YES	10	NO	YES
Pharmacological approaches – various								
Medical gases - Oxygen	YES	NO	YES	YES	YES	2	NO	YES

Pharmacological approaches - non-classified medications (i.e. experimental)								
Amino-oxyacetic acid	NO	NO	YES	YES	YES	2	NO	YES
Glutamate	NO	NO	YES	YES	YES	1	NO	YES
Neramexane	NO	NO	YES	YES	YES	6	NO	YES
Nerve growth factor	NO	NO	YES	YES	YES	2	NO	YES
Dextran 40	NO	NO	YES	YES	YES	1	NO	YES
Selurampanel	NO	NO	YES	YES	YES	1	NO	YES
Vestipitant	NO	NO	YES	YES	YES	1	NO	YES
Sound-based interventions								
Acoustic CR Neuromodulation	NO	YES	YES	YES	?	3	YES	YES
Amplification only devices	YES	YES	YES	YES	YES	8	YES	YES
Combination devices (i.e. combined amplification and sound generation)	YES	YES	YES	YES	YES	5	YES	YES
Phase-tailored sound treatment	NO	NO	YES	YES	NO	1	NO	YES
Sound generators only devices (sometimes referred to as 'maskers')	YES	YES	YES	YES	NO	20	YES	YES
Spectrally tailored sound treatment	NO	NO	YES	YES	NO	3	YES	YES
Auditory training	NO	YES	YES	YES	NO	4	NO	YES
Psychology-based interventions								
Cognitive/Behavioural approaches	YES	YES	NO	YES	YES	36	YES	YES
Counselling	YES	YES	NO	YES	NO	3	YES	YES

Complex interventions								
Heidleberg Neuro-Music Therapy	NO	NO	YES	YES	NO	2	NO	YES
Perceptual/Cognitive training	NO	NO	YES	YES	NO	4	NO	YES
Progressive Tinnitus Management	NO	YES	YES	YES	NO	4	NO	YES
Tinnitus Retraining Therapy	NO	YES	YES	YES	NO	9	YES	YES
Various – CBT plus biofeedback	NO	NO	YES	YES	NO	2	NO	YES
Various - CBT plus TRT (Cima)	NO	NO	YES	YES	NO	1	NO	YES
Magnetic stimulation								
Transcranial Magnetic Stimulation	NO	NO	YES	YES	NO	39	YES	YES
Various - electromagnetic stimulation of the ear	NO	NO	YES	YES	NO	1	NO	YES
Various – ear magnets	NO	NO	YES	YES	NO	1	NO	YES
Electrical stimulation								
Cochlear implants	NO	NO	YES	YES	NO	3	YES	YES
Transcranial Alternating Current Stimulation (tACS)	NO	NO	YES	YES	NO	1	YES	YES
Transcranial Direct Current Stimulation	NO	NO	YES	YES	NO	11	YES	YES
Transcutaneous electrical stimulation	NO	NO	YES	YES	NO	2	NO	YES
Vagus nerve stimulation	NO	NO	YES	YES	NO	2	YES	YES
Various – electrical stimulation of the ear (tympanic membrane)	NO	NO	YES	YES	NO	1	NO	YES

Various – electrical stimulation Via mastoid bones	NO	NO	YES	YES	NO	1	NO	YES
Various – electrical epidural stimulation of the cortex	NO	NO	YES	YES	NO	1	NO	YES
Manual physical therapy								
Cervical Spine Treatment	YES	NO	YES	YES	NO	2	NO	YES
Myofascial trigger point deactivation	NO	NO	YES	YES	NO	1	NO	YES
Temporomandibular joint treatment	YES	NO	YES	YES	NO	1	NO	YES
Relaxation or stress management								
Biofeedback/ Neurofeedback	NO	NO	YES	YES	NO	8	NO	YES
Hypnosis/ hypnotherapy	NO	NO	YES	YES	NO	3	NO	YES
Relaxation	YES	NO	YES	YES	NO	7	NO	YES
Complementary and alternative therapies								
Acupuncture	NO	NO	YES	YES	YES	26	YES	YES
Dietary supplements and herbal remedies – Alpha lipoic acid	NO	NO	YES	YES	YES	1	YES	YES
Dietary supplements and herbal remedies – Bu-Zhong-Yi-Qi	NO	NO	YES	YES	YES	1	YES	YES
Dietary supplements and herbal remedies – Caffeine	NO	NO	YES	YES	YES	1	YES	YES
Dietary supplements and herbal remedies – Gushen Pian	NO	NO	YES	YES	YES	1	YES	YES

Dietary supplements and herbal remedies – Hangekobokuto	NO	NO	YES	YES	YES	1	YES	YES
Dietary supplements and herbal remedies – Honeybee larvae	NO	NO	YES	YES	YES	2	YES	YES
Dietary supplements and herbal remedies – Korean Red Ginseng	NO	NO	YES	YES	YES	1	YES	YES
Dietary supplements and herbal remedies – Manganese	NO	NO	YES	YES	YES	1	YES	YES
Dietary supplements and herbal remedies – Homeopathy	NO	NO	YES	YES	YES	1	YES	YES
Laser treatment	NO	NO	YES	YES	YES	14	NO	YES
Ozone	NO	NO	YES	YES	YES	1	NO	YES
Ultrasound	NO	NO	YES	YES	YES	2	NO	YES
Vibratory stimulation	NO	NO	YES	YES	YES	2	NO	YES
Virtual reality	NO	NO	YES	YES	YES	1	NO	YES
Education and information								
Education and information	YES	YES	NO	YES	NO	8	NO	YES
Self-help interventions								
Support groups	YES	YES	YES	YES	NO	1	NO	YES